Treatment outcome with orthodontic aligners and fixed appliances: a systematic review with meta-analyses

Papageorgiou, Spyridon N ; Koletsi, Despina ; Iliadi, Anna ; Peltomaki, Timo ; Eliades, Theodore

Abstract: Background: The use of orthodontic aligners to treat a variety of malocclusions has seen considerable increase in the last years, yet evidence about their efficacy and adverse effects relative to conventional fixed orthodontic appliances remains unclear. Objective: This systematic review assesses the efficacy of aligners and fixed appliances for comprehensive orthodontic treatment. Search methods: Eight databases were searched without limitations in April 2019. Selection criteria: Randomized or matched non-randomized studies. Data collection and analysis: Study selection, data extraction, and risk of bias assessment was done independently in triplicate. Random-effects meta-analyses of mean differences (MDs) or relative risks (RRs) with their 95% confidence intervals (CIs) were conducted, followed by sensitivity analyses, and the GRADE analysis of the evidence quality.Results: A total of 11 studies (4 randomized/7 non-randomized) were included comparing aligners with braces (887 patients; mean age 28.0 years; 33% male). Moderate quality evidence indicated that treatment with orthodontic aligners is associated with worse occlusal outcome with the American Board of Orthodontics Objective Grading System (3 studies; MD = 9.9; 95% CI = 3.6-16.2) and more patients with unacceptable results (3 studies; RR = 1.6; 95% CI = 1.2-2.0). No significant differences were seen for treatment duration. The main limitations of existing evidence pertained to risk of bias, inconsistency, and imprecision of included studies. Conclusions: Orthodontic treatment with aligners is associated with worse treatment outcome compared to fixed appliances in adult patients. Current evidence does not support the clinical use of aligners as a treatment modality that is equally effective to the gold standard of braces.

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TITLE PAGE

Treatment outcome with orthodontic aligners and fixed appliances: a systematic review with meta-analyses

Spyridon N. Papageorgiou[1], Despina Koletsi[1], Anna Iliadi[2], Timo Peltomäki[3], Theodore Eliades[1]

[1] Clinic of Orthodontics and Pediatric Dentistry, Center of Dental Medicine, University of Zurich, Zurich, Switzerland

[2] Private practice, Athens, Greece

[3] Field of Dentistry, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

Correspondence to: Spyridon N. Papageorgiou, Clinic of Orthodontics and Pediatric Dentistry, Center of Dental Medicine, University of Zurich, Plattenstr. 11, 8032 Zurich, Switzerland. E-mail snpapage@gmail.com.

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ORCIDs

S.N. Papageorgiou: 0000-0003-1968-3326 / D. Koletsi: 0000-0001-6280-9372 / A. Iliadi: 0000-0001-9465-3202 / T. Peltomäki: 0000-0002-7938-1701 / T. Eliades: 0000-0003-2313-4979

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Summary

Background: The use of orthodontic aligners to treat a variety of malocclusions has seen considerable increase in the last years, yet evidence about their efficacy and adverse effects relative to conventional fixed orthodontic appliances remains unclear.

Objective: This systematic review assesses the efficacy of aligners and fixed appliances for the comprehensive orthodontic treatment.

Search methods: Eight databases were searched without limitations in April 2019.

Selection criteria: Randomized or matched non-randomized studies.

Data collection and analysis: Study selection, data extraction, and risk of bias assessment was done independently in triplicate. Random-effects meta-analyses of Mean Differences (MDs) or Relative Risks (RRs) with their 95% Confidence Intervals (CIs) were conducted, followed by sensitivity analyses, and the GRADE analysis of the evidence quality.

Results. A total of 11 studies (4 randomized / 7 non-randomized) were included comparing aligners with braces (887 patients; mean age 28.0 years; 33% male). Moderate quality evidence indicated that treatment with orthodontic aligners is associated with worse occlusal outcome with the American Board of Orthodontics Objective Grading System (ABO-OGS) (3 studies; MD=9.9; 95% CI=3.6 to 16.2) and more patients with unacceptable results (3 studies; RR=1.6; 95% CI=1.2 to 2.0). No significant differences were seen for treatment duration. The main limitations of existing evidence pertained to risk of bias, inconsistency, and imprecision of included studies.

Conclusions. Orthodontic treatment with aligners is associated with worse treatment outcome compared to fixed appliances in adult patients. Current evidence does not support the clinical use of aligners as a treatment modality that is equally effective to the gold standard of braces.

Registration: PROSPERO (CRD42019131589)

Key Words. malocclusion; orthodontics; efficacy; adverse effects; clinical trial; systematic review.

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Introduction

Rationale

The use of sequential clear aligners to treat malocclusion has seen a remarkable surge in the last decades and, fueled by aggressive marketing campaigns from manufacturers, a growing interest has been reported for such methods for invisible orthodontics, especially among adult patients.[1,2] A survey of Australian orthodontists in 2013 indicated that 73% of responders had used aligners to treat at least one case in the last year, with a median of 8 aligner cases.[3] A similar survey among Irish orthodontists in 2014 reported that 19% of them often used aligners to treat adult patients.[4] A large 2014 survey among orthodontic specialists in the States[5] revealed that 89% of them had treated at least one case with aligners (compared to 76% in 2008) with a median of 22 cases/year with aligners (compared to 12 cases/year in 2008), but only few orthodontists used aligners for premolar extraction cases (9%-18%). Additionally, another survey among members of the European Aligner Society indicated that 45% of orthodontists believed that aligners limit orthodontic treatment outcomes (even though the respective percentage among general dentists was only 5%).[6] These data might indicate that the initial surge of aligner treatment during its early years of fame might have now given its place to a more mature evaluation of this treatment modality, based on long-term outcomes.

Contrary to many medical fields, it is common place in orthodontics that novel marketed products and treatment approaches are clinically adopted based on advertisement policies, apparently without the appropriate clinical evidence to back any claims by the manufacturers.[7,8] In any case, it is imperative that alternative treatment methods offered to orthodontic patients are based on both the doctor's clinical expertise and solid evidence on the clinical performance of this modality. Ideally, treatment decisions should be based on well-designed and -reported comparative clinical trials on human patients and systematic reviews / meta-analyses thereof, after meticulous considerations of treatment efficacy and adverse effects.[9,10] Ample empirical evidence has now been gathered about the importance of proper study design and methodological characteristics that may result in bias.[11-16]

In the last decade several systematic reviews of clinical studies comparing orthodontic aligners with fixed appliances have emerged.[17-27] However, they all present methodological issues that may introduce

bias and hamper their ability to draw robust evidence-based recommendations, including: lack of an a priori design / pre-registered protocol,[18-21,25,26] language bias,[19,21,24] inclusion of non-randomized studies with uncontrolled confounding,[18,19,21,24-27] inadequate handing of the studies' risk of bias,[18-21,24-27] lack of quantitative data synthesis (meta-analysis),[18,19,21,24,26,27] improper data synthesis methods,[20,25] and being outdated.[18-20] Therefore, it is important that clinical practice is informed by a critical appraisal of currently available studies according to the principles of evidence-based medicine.

Objective

The aim of this systematic review was to critically assess the evidence derived from randomized clinical trials on humans undergoing orthodontic treatment to answer the question: Is there a difference in the treatment outcome with aligners compared to fixed appliances for comprehensive orthodontic treatment?

Materials and methods

Protocol and registration

This review's protocol was made a priori, registered in PROSPERO (CRD42019131589), and all post hoc changes were appropriately noted (Supplementary Table 1). This review is conducted and reported according to Cochrane Handbook[28] and PRISMA statement,[29] respectively.

Eligibility criteria

According to the Participants-Intervention-Comparison-Outcome- Study design (PICOS) schema and due to the scarcity of Randomized Clinical Trials (RCTs) on this subject, included were RCTs and non-randomized clinical studies on human patients of any age, sex, ethnicity, or malocclusion comparing full-arch orthodontic treatment with aligners and fixed appliances. No limitations concerning language, publication year or status were applied. Due to the scarcity of randomized trials on the subject, non-randomized studies were also included, with the requirement that the populations to be compared were matched regarding baseline malocclusion severity with objective measures like the Peer Assessment Rating (PAR) index[30] or the Discrepancy Index (DI)[31] from the American Board of Orthodontics (ABO). In particular, matching at the design stage was a pre- requisite for study inclusion, to eliminate baseline

confounding due to potential risk factors that might present a bearing on the outcome of interest. Matching was judged adequate when the Cohen's d for PAR or ABO DI between aligner and fixed appliance group at baseline was up to 0.3. Excluded were animal studies, case reports/series, non-clinical studies, and cross-sectional studies. Excluded were also studies without comprehensive orthodontic treatment, without two distinct treatment groups for aligners / fixed appliances, studies on previously-treated patients, studies without any outcome eligible for this review. The primary outcome for this review was the outcome of comprehensive orthodontic treatment judged with objective and reliable measures like the PAR index and the ABO's Objective Grading System (ABO-OGS) for dental casts and panoramic radiographs.[32] Secondary outcomes included treatment duration, as well as adverse effects like loss of periodontal support, External Apical Root Resorption (EARR), gingival recession, and proclination of the lower incisors during treatment.

Information sources and search

Eight electronic databases were searched systematically without any restrictions for publication date, language, or type from inception up to April 25, 2019 (Supplementary Table 2), while Directory of Open Access Journals (DOAJ), Digital Dissertations, metaRegister of Controlled Trials, WHO, and Google Scholar, as well as the reference/citation lists of eligible articles or existing systematic reviews were manually searched for any additions.

Study selection

Three authors (SNP, DK, AI) screened the titles and/or abstracts of studies retrieved from the searches to identify articles that potentially meet the inclusion criteria, before moving to their full-texts. Any differences between the two reviewers were resolved by discussion with the last author (TE).

Data collection process and items

Data collection from the identified reports was conducted using pre-defined and piloted forms covering: (a) study characteristics (design, clinical setting, country), (b) patient characteristics (age, sex), (c) malocclusion and treatment characteristics, (d) appliance type – including number of aligners and amount

of Interproximal Reduction (IPR) performed, (e) follow-up period, and (f) outcome details. Data were extracted by three authors (SNP, DK, AI) with the same way to resolve discrepancies as above.

Risk of bias of individual studies

The risk of bias of included studies was assessed according to Cochrane guidelines with the RoB 2.0 tool for randomized trials[33] and the ROBINS-I ("Risk Of Bias In Non-randomised Studies - of Interventions") tool for non-randomized studies.[34] Assessment of the risk of bias within individual trials was likewise performed independently by three authors (SNP, DK, AI), with the same way to resolve discrepancies consulting the last author (TE).

Data synthesis and summary measures

An effort was made to include all existing trials in the analysis; where data were missing, they were calculated by ourselves, requested from the authors or calculated from graphs (Supplementary Table 2). As the outcome of orthodontic treatment is bound to be affected by patient and treatment-related characteristics, a random-effects model was deemed appropriate to calculate the average distribution of true effects, based on clinical and statistical reasoning,[35] and a restricted maximum likelihood random-effects model was used according to recent guidance.[36] Mean differences (MDs) for continuous outcomes and relative risks (RRs) for binary outcomes and their corresponding 95% confidence intervals (CIs) were calculated as effect sizes. Statistically significant RRs were translated into Numbers Needed to Treat (NNTs) to gauge their clinical relevance.

The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and by calculating the τ^2 (absolute heterogeneity) and the I^2 statistics (relative heterogeneity), respectively. I^2 defines the proportion of total variability in the result explained by heterogeneity, and not chance, and we considered arbitrarily I^2 over 75% to represent considerable heterogeneity, while also considering the heterogeneity's direction (localization on the forest plot) and uncertainty intervals around heterogeneity estimates.[37] Ninety-five per cent predictive intervals were calculated for meta-analyses of ≥3 trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting, which are crucial for the correct interpretation of random-effects meta-analyses.[38]

Additional analyses and risk of bias across studies

Possible sources of heterogeneity were a priori planned to be sought through subgroup analyses and random-effects meta-regression in meta-analyses of at least 5 trials but could ultimately not be performed (Supplementary Table 2). Likewise, reporting biases were planned but ultimately not assessed, due to the limited number of meta-analyzed trials.

The overall quality of meta-evidence (ie, the strength of clinical recommendations) was rated using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach[39] following recent guidance on combining randomized with non-randomized studies[40] and summary of findings tables were constructed using the improved format proposed by Carrasco-Labra et al.[40] The minimal clinically important, large and very large effects were defined as half, one and two standard deviations of the posttreatment response (for continuous outcomes) and RRs of 1.5, 2.0 and 5.0 (for binary outcomes).[42,43] The produced forest plots were augmented with contours denoting the magnitude of the observed effects to assess heterogeneity, clinical relevance and imprecision.[44]

Robustness of the results was planned a priori to be checked with sensitivity analyses based on (a) inclusion/exclusion of non-randomized studies, (b) inclusion/exclusion of trials with methodological shortcomings, and (c) improvement of the GRADE classification. In the end, only one sensitivity analysis excluding non-randomized studies could be conducted.

All analyses were run in Stata version 14.0 (StataCorp LP, College Station, TX) by one author (SNP) and the dataset was openly provided.[45] All P values were two-sided with $\alpha = 5\%$, except for the test of between-studies or between-subgroups heterogeneity where α-value was set as 10%.[46]

Results

Study selection

The electronic literature search yielded 1376 results, while another seven were manually identified from the reference/citation lists of identified papers (Figure1). After duplicate removal and screening the titles/abstracts of identified reports, the full texts of 343 papers were checked against the eligibility criteria (Supplementary Table 3). Ultimately, 11 papers pertaining to 11 unique studies (4 randomized and 7

retrospective non-randomized) were finally included, which were published as journal papers of dissertation/theses.

Study characteristics

The included studies were conducted in university clinics (n=6; 55%), private practices (n=4; 36%), or hospitals (n=1; 9%) and originated from six different countries (Canada, China, Ireland, Italy, South Korea, and the United States of America) (Table 1). A total of 446 and 443 patients were treated with aligners and fixed appliances, respectively, with a median total sample of 66 patients per included study (range 19 to 200 patients per study). Out of the seven studies reported on patient sex, 215 of the 661 patients in total were male (33%), while the mean patient age out of the nine studies reporting this was 28.0 years.

As far as complexity of the treated cases is concerned, only six studies (55%) reported this with either the PAR index (n=3; 27%) or the ABO DI (n=3; 27%). Eight of the studies (73%) performed non-extraction treatment, one study (9%) both extraction and non-extraction treatment, and one study (9%) extraction treatment. The majority of studies (9 /11 studies; 82%) reported on conventional comprehensive treatment, while one study (9%) reported on orthodontic treatment of patients with history of periodontal disease and one study (9%) reported on combined orthodontic/orthognathic treatment. Details of the aligner treatment were only partly reported among the included studies with only 2 studies (18%) reporting the number of aligners, 4 studies (36%) reporting on 'refinement' rate (i.e. the mid-course re-evaluation and planning of additional aligners), and 2 studies (18%) on the actual amount of interproximal enamel reduction performed during treatment in both groups.

The included studies reported on a wide spectrum of treatment outcomes, with only 3 studies reporting on the complete ABO-OGS score including all 8 components, as well as failure of the case to pass the ABO criteria for adequate occlusal results (ABO-OGS score < 30 points). One study reported on the ABO-OGS score of 7 out of 8 components (excluding root angulation) and also excluded scoring the second molars without any justification. One study also reported solely on 2 of the 8 ABO-OGS components – namely marginal ridges and buccolingual inclination. Three studies used the PAR index and reported either post-treatment PAR scores or PAR reductions. Eight studies reported on treatment duration, though

considerable variation in the reported results was seen. Finally, single studies reported on periodontal probing depth, alveolar bone loss, EARR, lower incisor inclination, and gingival recessions.

Risk of bias within studies

The included randomized trials presented several issues that increased their risk for bias (Supplementary Table 4). Two trials were in high risk of bias due to problems in the randomization process, deviations from intended interventions, missing outcome data, and outcome measurement. The remaining two trials were in low risk of bias, except from the fact that no a priori trial protocol could be found to rule out selective reporting. The included non-randomized studies were in considerably higher risk of bias (Supplementary Table 5), with 5 of them presenting moderate risk of bias, one of them serious risk of bias, and one of them critical risk of bias. Their main shortcomings pertained to confounding, selection of participants into the study, deviations from intended interventions, outcome measurement, and selection of the reported result).

Data synthesis

For all included studies the data reported in the paper were used, while for one study without matching[51] the author provided raw data that were used to extract a matched sub-sample to include (Supplementary Table 6). The results of all individual trials and the results of the meta-analyses of at least 2 studies are found in Supplementary Table 7 and Table 2.

Fourteen different meta-analyses could be conducted pertaining to the review's primary outcome (ABO-OGS scores), PAR scores, and treatment duration. A meta-analysis of three studies indicated that treatment with aligners was associated with significantly worse ABO-OGS scores compared to braces (MD=9.9 points greater; 95% CI=3.6 to 16.2 points greater; P=0.002), which was also clinically relevant (Table 3; Figure 2). Considerable heterogeneity was seen among the three included studies (I^2=84%), which meant that several patient-related or treatment-related factors might play a role in the actual final occlusal result. However, existing heterogeneity influenced only the precise calculation of the difference between aligners and fixed appliances, as one study indicated a moderate difference and the other two indicated a large one. It did not however influence the direction of the effect, as all three studies showed that fixed appliances were significantly associated with better treatment results than aligners.

Additionally, patients treated with aligners were significantly more likely to be finished to an unacceptable quality according to the ABO standards and fail the ABO examination criteria (ABO-OGS score > 30) compared to those treated with braces (3 studies; RR=1.6; 95% CI=1.2 to 2.0; P<0.001; Table 3; Supplementary Fig 1). No considerable heterogeneity across studies was seen, which reported a small to moderate increase in the rate of suboptimal finishing quality. On absolute terms these corresponded to ABO 'fail rates' of 60.6% and 38.9% for aligners and braces, respectively (Supplementary Fig2). This is translated to an NNT of 5, which means that every fifth case treated with aligners instead of fixed appliances would fail the ABO examination, but would get a 'passing' grade if it was treated with fixed appliances, which is a potentially clinically relevant effect.

Looking at the comparative performance for each separate component of ABO-OGS between aligners and braces gives a more precise image about the occlusal aspects mostly affected by the treatment modality (Table 3; Figure 3). Overall, meta-analyses of three studies indicated that 5 of the 8 aspects of the occlusion were significantly better finished with fixed appliances than with aligners: buccolingual inclination (MD: 0.8 point; 95% CI: 0.5 to 1.1 point; P<0.001), occlusal contacts (MD: 3.1 points; 95% CI: 0.6 to 5.6 points; P=0.02), occlusal relationship (MD: 1.0 point; 95% CI: 0.6 to 1.4 points; P<0.001), overjet (MD: 1.8 points; 95% CI: 0.6 to 3.0 points; P=0.002), and root angulation (MD: 0.8 point; 95% CI: 0.5 to 1.1 point; P<0.001). Looking carefully at the effect magnitude it is obvious that the clinical relevance for each separate criterion is questionable, as small to moderate differences between aligners and braces are seen on average. However, when adding all these differences for each criterion, a clinically relevant worse treatment outcome is seen with aligners overall.

Looking at the occlusal outcome of treatment through meta-analyses using the PAR index gives a slightly different picture (Table 3). Overall, no statistically significant difference between aligners and braces was detected either by post-treatment absolute values (2 studies; P=0.98) or by PAR reduction (3 studies; P=0.06).Likewise, no difference in the proportion of patients experiencing a great improvement in their PAR scores through treatment (PAR reduction of at least 22 points or PAR score of 0 post-treatment) was seen (2 studies; P=0.26).

Considerable variation was seen in the effect of treatment modality on treatment duration. Meta-analysis of seven studies indicated that on average no definite conclusions can be drawn regarding

treatment duration with either aligners or fixed appliances (MD: -0.6 month; 95% CI: -3.7 to 2.6 months; P=0.73). Extreme heterogeneity was seen across studies (I^2=94%), which makes the ability to synthesize existing studies into a single estimate questionable (Figure 4). Specifically, two studies reported statistically significant reduction in treatment duration with aligners, two studies reported statistically significant increase in treatment duration with aligners, while the remaining three studies did not find statistically significant differences. Furthermore, exclusion of a study assessing combined orthodontic/orthognathic treatment[56] instead of only orthodontic treatment did not improve the results (6 studies; MD: -0.1 month; 95% CI: -3.5 to 3.4 months; I^2=95%). Nor was the situation improved by limiting the meta-analysis to only randomized trials (2 studies; MD: 2.69 months; 95% CI: -5.0 to 10.4 months; I^2=96%) or to only studies with non-extraction treatment (5 studies; MD: 0.6 month; 95% CI: -3.2 to 4.4 months; I^2=96%). Therefore, it is logical to assume that treatment duration is influenced by additional confounding variables and that the choice of appliance alone does not show a consistent effect on treatment duration.

Results of individual studies

Additionally, several outcomes were assessed by single studies that provide only limited insights (Supplementary Table 7). Results of a single study[50] indicated that aligners were worse in terms of reduction for the PAR component for upper anteriors (MD: -1.0 point; 95% CI: -1.9 to -0.1 point; P=0.02) and overbite (MD: -1.0 point; 95% CI: -1.9 to -0.2 points; P=0.02) compared to braces. The results of a single study[50] indicated that aligners were more efficient in terms of PAR reduction / month of treatment compared to fixed appliances (MD: 0.4 point/month; 95% CI: 0.1 to 0.7 point/month; P=0.01). However, as the same study reported that aligners were overall associated with smaller reductions in the PAR scores than fixed appliances, looking at the PAR reduction / month might be misleading.

As far as adverse effects of treatment are concerned, a single identified study on EARR[57] reported that significantly smaller percentage of the incisors' root was resorbed during treatment compared to fixed appliances (MD: -1.8%; 95% CI: -2.4% to -1.3%; P<0.001; Table 4). The same was seen for the various subgroups according to tooth type (central versus lateral incisor) and jaw (maxilla versus mandible), but the effect magnitude was on average very small and probably of no clinical relevance. Additionally, treatment with aligners was not associated in a single included study[52] with significantly lower proclination of the lower

incisors compared to fixed appliances (P=0.10). However, it must be noted that a very small sample was included, which makes the study probably underpowered to identify such a small difference of 1.9º between groups, if it really exists. Furthermore, no significant difference in the development of gingival recessions 2 years after treatment with aligners or fixed appliances was seen in another single study (MD: 0.9; 95% CI: 0.3 to 2.7; P=0.86).[53]

Finally, limited evidence on the effect of appliance choice on loss of periodontal attachment was provided by a single identified study,[51] which assessed orthodontic alignment of anterior teeth in adult patients with previous history of treated periodontal disease and found no differences between aligners and braces for periodontal probing depth (P=1.00) or alveolar bone levels (P=0.69). On the other side, fixed appliances were significantly quicker repositioning the patients' migrated anterior teeth compared to aligners (3.9 versus 6.0 months; MD: -2.1 months; 95% CI: -3.7 to -0.5 months; P=0.01).

Additional analyses, risk of bias across studies, and quality of evidence

Several subgroup analyses, meta-regressions, and assessments for reporting biases were originally planned in the review's protocol, but could ultimately not be performed due to limited data and inadequate reporting (Supplementary Table 1).

The quality of evidence for the 7 meta-analyses on bracketed teeth ranged from high to very low, as methodological limitations introducing bias, inconsistency, and imprecision were identified on some cases (Table 3). The two meta-analyses with significant differences in the ABO-OGS scores were supported by evidence of moderate quality, which indicates that these results are likely to be close to the estimate of the true effect. A GRADE rating of low was assigned to the significant difference in EARR, which however might be markedly different from the estimate of the true effect. Finally, the remaining 5 non-significant meta-analyses were supported by evidence of moderate to very low quality. The main reason for downgrading the quality of evidence pertained to the inclusion of non-randomized studies with serious / critical methodological issues that most probably introduce bias. This was especially seen in the retrospective study of Gu et al.[50] that selectively reported data from what might be regarded as 'good' cases, while excluding patients with issues of compliance or oral hygiene. This means that further research in

terms of well-designed studies is very likely to have an important impact, which is likely to change our current estimates of effect.

Sensitivity analysis

The sensitivity analyses by omitting non-randomized studies indicated relative robustness of the results (Supplementary Table 8), apart from the observed reduced statistical power of the sensitivity analyses, which was expected after omitting trials.

Discussion

Summary of evidence

The current systematic review summarizes evidence from randomized trials and matched non-randomized studies on treatment outcome with orthodontic aligners or braces. Out of the initially identified 1376 hits from the literature search, 11 trials (involving 887 patients) were ultimately included.

Robust evidence from meta-analyses of overall ABO-OGS scores, individual ABO-OGS components, and proportion of treated cases with 'acceptable' finishing quality (ABO-OGS score < 30) indicated that treatment with aligners is associated with worse treatment outcome compared to braces (Table 2). It has been previously reported that it is considerably more difficult to control root movement with aligners compared to fixed appliances, especially without the use of attachments.[2,57,58] Root movement is presumably better facilitated by adding ellipsoid precision attachments that can produce couples,[2] which remains to be tested experimentally. On the other side, three ABO-OGS components (alignment, marginal ridges, and interproximal contacts) gave very similar results for both modalities. This is not surprising, since aligners are known to consistently produce adequate space closure of up to 6 mm by progressively tipping teeth into spaces in small increments and can successfully straight dental arches by derotating teeth, especially when composite attachments are bonded.[58-60]

On the other side, the PAR index revealed on the whole no significant differences between aligners and braces, with the exception of an almost significant difference in PAR reduction (P=0.06; Table 2) and significant differences in the PAR components for upper anteriors and overbite (P<0.05; Supplementary Table7) that favored braces. This discrepancy between the results of the ABO-OGS and the PAR index

can be explained by integral differences between components of the two tools. The PAR index was developed to assess in a systematic manner the outcome of orthodontic treatment in order to be incorporated in both quality assessment measures of orthodontic care and scientific research. It provides however a vague assessment of the occlusion and disregards aspects like tooth inclination, remaining spaces, and alignment of the posterior dental arch, which are important variables for board examination cases.[32] It does not provide a detailed assessment of the tooth relationship within an ideal dental arch as the ABO-OGS does, which was developed in order to assess the fine details expected to see in a meticulously finished case in all three planes (first, second, and third order). Reported limitations of the PAR index[61] include among others a low weighting for overbite scores and high weighting for overjet scores.[62] Indeed, post-treatment PAR scores do not correlate significantly with post-treatment ABO-OGS scores.[63,64] Subsequently, the PAR index has been widely used to also assess the baseline severity of a case. However, the PAR index to this end does not consider aspects like skeletal discrepancies / cephalometric values, developmental tooth anomalies, ectopic teeth, or soft tissues relationships and again does not correlate well with the ABO DI.[63]

Overall and especially with regard to orthodontic treatment outcomes, it is apparently straightforward that the clinician's expertise might play a significant role not only with regard to the selection of the most appropriate treatment modality for each case, but is also closely linked to the administered quality of treatment outcomes, as performed by the operators/ clinicians. As such, efforts for future research should be directed not only towards high quality randomized trials that may mitigate bias stemming from extra- operator predictors such as patients' clinical characteristics or levels of response/ compliance, but also towards studies streamlining the effect of different levels of clinician's expertise to the retrieved treatment outcomes.

Data synthesis on treatment duration with aligners or braces was not possible to be robustly conducted, since a very heterogeneous image emerged (Figure 4). There exist both studies that favor one or the other appliance with significant differences, as well as studies that show no significant difference (Figure 4). Therefore, it is logical to assume that appliance choice alone is not sufficient to considerably dictate treatment duration and other factors need to be taken carefully into account in future studies like

baseline severity, extractions, number of aligners/ refinements, and standard of care to which patients are treated.

As far as adverse effects of treatment are concerned, a single identified study on EARR[57] reported that significantly smaller percentage of the incisors' root was resorbed during treatment compared to braces (MD: -1.8%; P<0.001; Table 4). It must also here be stressed out that evaluation of EARR during treatment is complicated, since many risk factors come into play including the patient's genetic predisposition towards EARR,[65] the chosen mechanotherapy,[66] the duration of treatment,[67] and the actual amount of tooth movement (and especially apical movement).[65] A carefully conducted retrospective non-randomized study taking confounders like baseline severity through ABO DI, genetic polymorphisms, and absolute apical displacement into account concluded that treatment with orthodontic aligners results in similar amounts of EARR compared to fixed appliances. Therefore, it might be prudent to check if any significant differences in EARR reported in the literature are not rather due to teeth being actually moved less around with aligners.

Furthermore, no significant difference in the development of gingival recessions 2 years after treatment with aligners or fixed appliances was seen in another single study (P=0.86).[53] It might be expected that choice of appliance alone might not directly influence the development of gingival recession. Even if appliance choice was associated with increased anterior anchorage loss/ incisor proclination (which was not seen), this would not necessarily translate to increased risk of gingival recession.[68,69] Although orthodontic treatment on average increases the risk for gingival recessions,[70] its precise etiology is multifactorial with risk factors including periodontal disease, mechanical trauma, patient age, smoking, and induction of bone dehiscences by positioning the teeth beyond the limits of the alveolar plate.[69,71]

Finally, limited evidence on the effect of appliance choice on loss of periodontal attachment was provided by a single identified study,[51] which assessed orthodontic alignment of anterior teeth in adult patients with previous history of treated periodontal disease. After retrieving raw data from the author and matching the study's groups for baseline status, no differences between aligners and fixed appliances were seen for periodontal probing depth (P=1.00) or alveolar bone levels (P=0.69). On the other side, fixed appliances were significantly quicker repositioning the patients' migrated anterior teeth compared to aligners (3.9 versus 6.0 months; P=0.01). It must be noted that although previous systematic reviews of mostly methodologically compromised studies have reported that aligners might be associated with

facilitation of better oral hygiene than fixed appliances,[17,22,54] a recent randomized clinical trial[72] found no significant and consistent advantage in terms of plaque index, gingival index, or periodontal bleeding index between patients treated with aligners and fixed appliances. Therefore, fixed appliances can also be compatible with proper oral hygiene.

Strengths and limitations

This systematic review has several strengths, comprising an a priori registered protocol,[15] a comprehensive literature search, the inclusion of randomized or matched non-randomized studies, the use of modern analytic methods,[36] the application of the GRADE approach to assess the strength of provided recommendations,[39] and the transparent provision of all data.[73]

Some limitations also do exist in the present review. For one, methodological issues existed for all included studies that might influence conclusions, and this is especially the case for included retrospective non-randomized studies.[11,13] influence conclusions, and this is especially the case for included retrospective non-randomized studies.[11,13] Selection bias may not be ruled out when non- randomized designs are used; however, in an attempt to reduce the risk for such a potential limitation due to dissimilarity of groups under comparison, we solely included studies with populations matched for baseline characteristics. Inclusion of non-randomized studies in meta-analysis is not considered prohibitory, provided robust bias appraisal has been performed, and recent guidance has been provided about how to appropriately incorporate such designs.[40] Also, a heterogeneous response among studies was seen for many outcomes, which is to be expected due to the wide spectrum of malocclusions, appliances, and clinical settings included. This heterogeneity affected however mostly the magnitude and not the direction of the effects, except from the outcome of treatment duration, where no consistent effect of appliance choice could be seen. Furthermore, most meta-analyses were based predominantly on small trials, which might affect the precision of the estimates.[74] Additionally, the small number of trials that were ultimately included in the meta-analyses and their incomplete reporting of results and potential confounders like level of case severity, oral hygiene, compliance, use of bonded attachments, number of aligners, rate of refinement need, or amount of interproximal enamel reduction precluded the conduct of many analyses for subgroups and meta-

regressions that might enable identification of patient subgroups for which aligners might be an equal or even more appropriate treatment alternative compared to fixed appliances.

Conclusions

According to currently existing clinical evidence from randomized trials and matched non-randomized studies on mostly adult patients with mild to severe malocclusions treated with or without extractions, it seems that orthodontic treatment with aligners is associated with worse treatment outcomes compared to fixed appliances. Treatment duration does not seem to be defined by appliance alone and patient or treatment-related factors might come into play. For adverse outcomes such as EARR, proclination of lower incisors and development of gingival recessions, further individual well- conducted trials are welcome and should be at stake in order to draw robust conclusions.

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Conflicts of interest

None to declare.

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Figure 1. PRISMA flowdiagram for the identification and selection of eligible studies in this review.

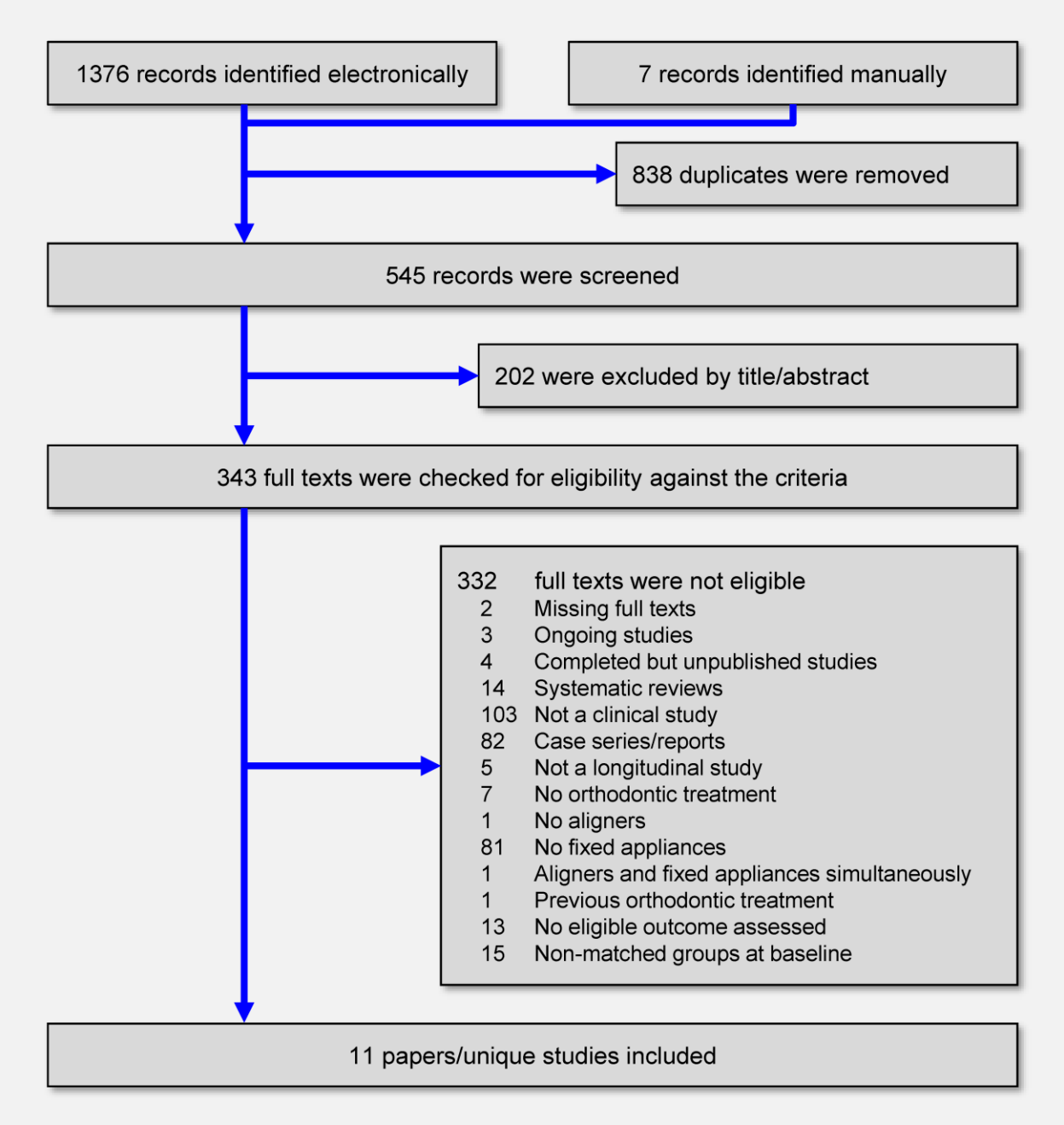

Figure 2. Contour-enhanced forest plot on the comparison of total ABO-OGS scores post-treatment between aligners and fixed appliances. ABO-OGS, American Board of Orthodontists Objective Grading System; AL, aligner; CI, confidence interval; FX, fixed appliance; M, mean; MD, mean difference; N, number of patients; SD, standard deviation. Contours correspond to different effect magnitude and the red dotted line corresponds to 95% random-effects prediction.

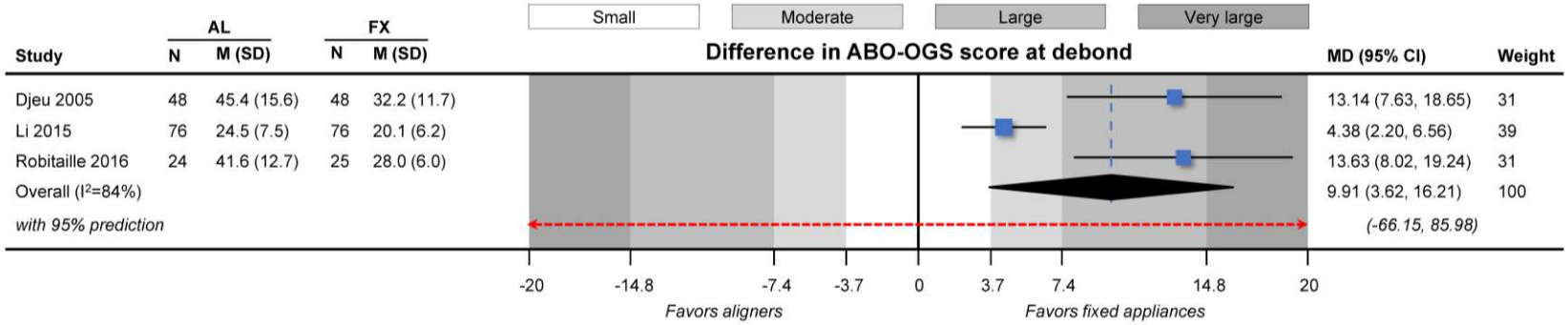

Figure 3. Composite contour-enhanced forest plot illustrating the summary results of 8 meta-analyses (each with 3 studies and 297 patients) for the comparison of each separate ABO-OGS component between orthodontic aligners and fixed appliances. ABO-OGS, American Board of Orthodontists Objective Grading System; CI, confidence interval; MD, mean difference. Contours correspond to different effect magnitude and the red dotted lines correspond to 95% random-effects predictions.

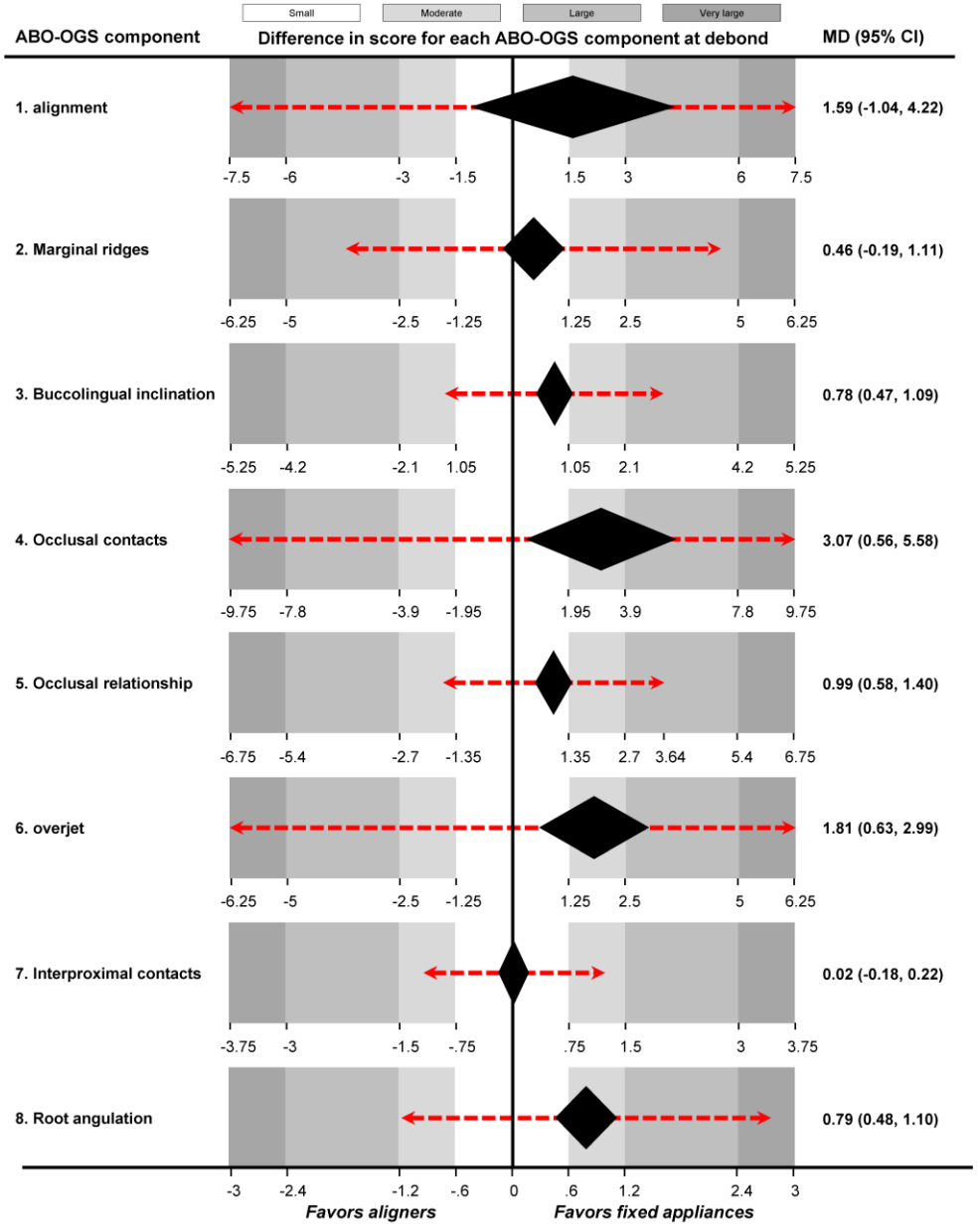

Figure 4. Contour-enhanced forest plot on the comparison of treatment duration in months between aligners and fixed appliances. AL, aligner; CI, confidence interval; FX, fixed appliance; M, mean; MD, mean difference; N, number of patients; SD, standard deviation. Contours correspond to different effect magnitude and the red dotted line corresponds to 95% random-effects prediction.

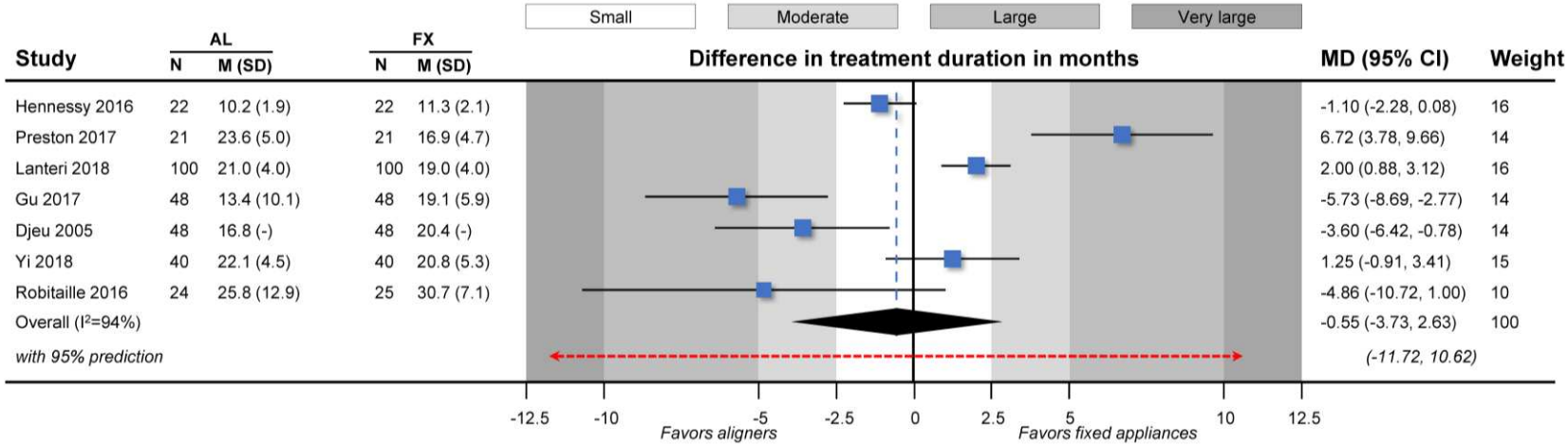

Table 1. Characteristics of included studies.

Study	Design; setting; country*	Patients (M/F); age†	Malocclusion / Tx	Appliance	Aligners / refinement / IPR (mm)	FU (mos)	Outcome
Abbate 2015[47]	RCT; Uni; ITA	AL: 25 (NR); (10-18) FX: 22 (NR); (10-18)	NR / Non-Ex	AL: Invisalign® FX: Labial CLB	NR / NR / NR	BL, 3.0, 6.0, 9.0, 12.0 mos in Tx	PPD
Djeu 2005[48]	rNRS; Pract; USA	AL: 48 (NR); 33.6 FX: 48 (NR); 23.7	DI: 19.3; Ex & Non-Ex	AL: Invisalign® FX: Labial CLB (TE)	NR / NR / allowed	BL, END	$ABO\text{-}OGS_8$; TxDur
Fetouh 2008[49]	rNRS; Pract; USA	AL: 33 (NR); NR FX: 33 (NR); NR	Cl. I; mild crowding & overbite; DI: 3.22 / Non-Ex	AL: Invisalign® FX: Labial CLB	NR / NR / NR	BL, END	$ABO\text{-}OGS_7$
Gu 2017[50]	rNRS; Pract; USA	AL: 48 (16/32); 26.0 FX: 48 (18/30); 22.1	PAR: 21.8; compliant / Non-Ex	AL: Invisalign® FX: Labial CLB (SW)	NR / 38% / NR	BL, END	PAR; TxDur
Han 2015[51]	rNRS; Uni; KOR	AL: 10 (2/8); 51.2 FX: 9 (4/5); 47.3	Previous PerioDis; DI: 4.4 / Non-Ex	AL: NR FX: Labial CLB	NR / NR / allowed	BL, END	ABL; PPD; TxDur
Hennessy 2016[52]	RCT; Hosp; IRL	AL: 20 (6/14); 29.1 FX: 20 (7/13); 23.7	Mild crowding / Non-Ex	AL: Invisalign ® FX: Labial SLB (MBT)	18 ALs / allowed / AL:FX 1.9:1.5	BL, END	IMPA; TxDur
Lanteri 2018[53]	rNRS; Pract; ITA	AL: 100 (30/70); 28.0 FX: 100 (30/70); 25.0	PAR: 23.3 / Non-Ex	AL: Invisalign ® FX: Labial SLB (MBT)	43 ALs‡ / 37% / AL:FX 1.3:1.5	BL, END, 24.0 mos Post-Tx	PAR; RetFail; GingRec
Li 2015[54]	RCT; Uni; CHN	AL: 76 (27/45); 35.2 FX: 76 (27/45); 32.2	DI: 27.4 / Ex	AL: Invisalign® FX: Labial CLB	NR / NR / allowed (AL)	BL, END	$ABO\text{-}OGS_8$; TxDur
Preston 2017[55]	RCT; Uni; USA	AL: 22 (10/12); 27.8 FX: 22 (7/15); 25.4	Cl. I; mild crowding / Non-Ex	AL: Invisalign® FX: Labial CLB (ALX)	NR / 100% (2 refinements) / NR	BL, END, 1.0, 6.0 mos Post-Tx	$ABO\text{-}OGS_2$; TxDur; contact areas
Robitaille 2016[56]	rNRS; Uni; CAN	AL: 24 (11/13); 29.8 FX: 25 (6/19); 23.4	DI: 31.5 / orthognathic surgery	AL: Invisalign® FX: Labial CLB	NR / NR / NR	BL, END	$ABO\text{-}OGS_8$; TxDur
Yi 2018[57]	rNRS; Uni; CHN	AL: 40 (9/31); 21.8 FX: 40 (11/29); 23.3	PAR: 22.6 / Non-Ex	AL: NR FX: Labial CLB	NR / 65% / NR	BL, END	PAR; TxDur; EARR

* countries given with their alpha-3 codes.

† patient age is given either as mean (one value in without parenthesis) or if mean isn't reported as range (two values in parenthesis).

‡ including refinement aligners

ABL, alveolar bone level; ABO-OGS, American Board of Orthodontists Objective Grading System (number of components assessed given in subscript); AL, aligner; ALX, Alexander technique; BL, baseline; Cl., (Angle's) Class; CLB, conventionally ligated brackets; DI, discrepancy index; EARR, external apical root resorption; END, end of comprehensive treatment; Ex, extraction; FU, follow-up; FX, fixed appliance; GingRec, gingival recession; Hosp, hospital; IMPA, inclination of lower incisors to mandibular plane; IPR, interproximal enamel reduction; M/F, male / female; MBT, MacLaughlin-Bennet-Trevisi prescription; mo, month; NR, not reported; PAR, peer assessment rating; PerioDis, periodontal disease; PPD, periodontal probing depth; Pract, private practice / clinic; RCT, randomized clinical trial; SLB, self-ligating bracket; SW, straightwire; TE, Tip-Edge; Tx, treatment; TxDur, treatment duration; Uni, university clinic.

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Table 2. Results of random-effects meta-analyses for eligible outcomes with at least two contributing studies comparing aligners to fixed appliances.*

Outcome*	n	Effect	P	I^2 (95% CI)	tau^2 (95% CI)	95% prediction
ABO-OGS total score	**3**	**MD: 9.91 (3.62, 16.21)**	**0.002†**	**84% (38%, 99%)**	**25.52 (3.01, 507.80)**	**-66.15, 85.98**
ABO-OGS failure (score>30)	3	RR: 1.56 (1.23, 1.98)	<0.001†	0% (0%, 91%)	0 (0, 0.55)	0.33, 7.32
ABO-OGS component 1: alignment	3	MD: 1.59 (-1.05, 4.22)	0.24	91% (60%, 100%)	4.93 (0.71, 95.19)	-31.38, 34.55
ABO-OGS component 2: marginal ridges	3	MD: 0.46 (-0.18, 1.10)	0.16	0% (0%, 88%)	0 (0, 2.52)	-3.68, 4.61
ABO-OGS component 3: buccolingual inclination	3	MD: 0.78 (0.46,1.09)	<0.001†	0% (0%, 94%)	0 (0, 3.77)	-1.26, 2.81
ABO-OGS component 4: occlusal contacts	3	MD: 3.07 (0.57, 5.57)	0.02†	79% (19%, 99%)	3.78 (0.24, 79.63)	-26.47, 32.61
ABO-OGS component 5: occlusal relationship	3	MD: 0.99 (0.58, 1.40)	<0.001†	0% (0%, 94%)	0 (0, 7.24)	-1.66, 3.64
ABO-OGS component 6: overjet	3	MD: 1.81 (0.64, 2.98)	0.002†	50% (0%, 97%)	0.54 (0, 17.35)	-10.25, 13.87
ABO-OGS component 7: interproximal contacts	3	MD: 0.02 (-0.16, 0.21)	0.82	0% (0%, 89%)	0 (0, 0.74)	-1.18, 1.22
ABO-OGS component 8: root angulation	3	MD: 0.79 (0.49, 1.10)	<0.001†	0% (0%, 89%)	0 (0, 0.65)	-1.18, 2.76
PAR post-Tx	2	MD: -0.03 (-2.02, 1.96)	0.98	83% (0%, 100%)	1.72 (0, 258.55)	NC
PAR reduction via Tx	3	MD: -1.76 (-3.62, 0.10)	0.06	41% (0%, 96%)	1.13 (0, 42.78)	-19.88, 16.36
PAR great improvement (reduction>30)	2	RR: 0.72 (0.40, 1.28)	0.26	66% (0%, 100%)	0.12 (0, 22.56)	NC
Treatment duration (months)	7	MD: -0.55 (-3.73, 2.63)	0.73	94% (82%, 99%)	16.25 (4.74, 73.67)	-11.72, 10.62

ABO-OGS, American Board of Orthodontists Objective Grading System; CI, Confidence Interval; MD, Mean Difference; n, number of contributing studies; NC, Non-Calculable; PAR, Peer Assessment Rating; RR, Relative Risk.

† statistically significant findings at the 5% level.

* with bold are given meta-analyses being both statistically significant and clinically relevant – judged as having an effect being at least equal to the average standard deviation of the control (fixed appliance) group across included studies or a relative risk of at least 2.

Table 3. Summary of findings table according to the GRADE approach.

Outcome [follow-up] Studies (patients)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Quality of the evidence (GRADE)[b]	What happens with aligners
		Fixed appliance[a]	Aligners	Difference in aligner group		
ABO-OGS score [post Tx] 297 patients (3 studies)	-	26.7 pts	-	9.9 pts greater (3.6 to 16.2 greater)	⊕⊕⊕◯ moderate[c,d,e] due to bias	Probably leads to worse finishing quality (higher ABO-OGS scores)
Unacceptable finishing quality (ABO-OGS score>30 pts) [post Tx] 297 patients (3 studies)	RR 1.6 (1.23 to 1.98)	38.9%	60.6% (47.8%-77.0%)	21.7% more (8.9% to 38.0% more)	⊕⊕⊕◯ moderate[c] due to bias	Probably leads to more patients with unacceptable finishing quality
PAR reduction [post Tx] 376 patients (3 studies)	-	19.5 pts	-	1.8 pts less (3.6 less to 0.1 more)	⊕⊕◯◯ low[f] due to bias	Little to no difference in treatment efficacy (smaller reduction in PAR scores)
Great improvement in PAR (PAR reduction>30 pts) [post Tx] 296 patients (2 studies)	RR 0.7 (0.40 to 1.28)	46.0%	33.0% (18.5%-58.8%)	13.0% less (27.5% less to 12.8% more)	⊕⊕◯◯ low[f] due to bias	Little to no difference in patients with great improvement in PAR scores
Treatment duration [post Tx] 607 patients (7 studies)	-	19.6 mos	-	0.6 mo shorter (3.7 shorter to 2.6 longer)	⊕◯◯◯ very low[g,h] due to bias, inconsistency	Too heterogenous response to synthesize across studies
EARR as % of anteriors' root length [post Tx] 80 patients / 640 teeth (1 study)	-	7.0%	-	1.8% less (1.3% to 2.4% less)	⊕⊕◯◯ low[f] due to bias	Might lead to greater EARR
Inclination of lower incisors [near Tx end] 44 patients (1 study)	-	5.3°	-	1.9° less (4.1° less to 0.3° more)	⊕⊕◯◯ low[i,j] due to bias, imprecision	Little to no difference in lower incisor inclination
Gingival recession [2 years post Tx] 158 patients (1 study)	RR 0.9 (0.31 to 2.68)	8.0%	7.2% (2.5%-21.4%)	0.8% less (5.5% less to 13.4% more)	⊕⊕⊕◯ moderate[c] due to bias	Little to no difference in gingival recession

Intervention: comprehensive orthodontic treatment with thermoplastic aligners versus fixed appliances / Population: adolescent or adult patients with any kind of malocclusion / Setting: university clinics, private practice, hospital (Canada, China, Ireland, Italy, USA).

[a] Response in the control group is based on average response of included studies (random-effects meta-analysis).

[b] Starts from "high"

[c] Downgraded by one level for bias due to the inclusion of non-randomized studies with moderate risk of bias

[d] No downgrading for inconsistency (even though I^2>75%), as it affects only our estimate about the difference between treatment modalities, but not our decision (all studies are on the right side of forest plot and show significant effects).

[e] Potentially great effect observed (larger than one average standard deviation), but no upgrading due to residual confounding.

[f] Downgraded by two levels for bias due to the inclusion of non-randomized studies with critical / serious risk of bias.

[g] Downgraded by two levels for bias due to the inclusion of randomized trials with high risk of bias and non-randomized studies with serious/critical risk of bias.

[h] Downgraded by one level due to inconsistency; great variability is seen among included studies with significant studies arranged on both sides of the forest plot (confident signs of heterogeneity that influence our decision about which treatment is shorter, which precludes calculating an average effect)

[i] Downgraded by one level for bias due to the inclusion of a randomized trial with high risk of bias.

[j] Downgraded by one levels for imprecision due to the inclusion of an inadequate sample.

ABO-OGS, American Board of Orthodontists Objective Grading System; CI, confidence interval; EARR, external apical root resorption; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PAR, peer assessment rating; pt, point; Tx, treatment

SUPPLEMENTAL MATERIAL

Supplementary Table 1. Additional review details and deviations from protocol.

Additional details

- Pre/Post Correlations: A Pre/Post correlation for 'change in PAR' in the aligner (0.50) and fixed appliance group (0.27) was back-calculated from the data of Yi et al., 2018. A Pre/Post correlation for 'change in PPD' in the aligner (0.78) and fixed appliance group (0.90) was back-calculated from the data of Han, 2015.
- The 'changes from baseline in PPD' for the study of Abbate et al., 2015 and the 'change from baseline in PAR' for the study of Lanteri et al., 2018 were calculated using the above-mentioned pre/post correlations.
- Data provided only in graphs was extracted with WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/). We extracted baseline DI scores from a graph in the Fetouh 2008 study with this mehod.

Deviations from protocol

- Several factors were planned to be assessed through subgroup analyses/metaregressions in meta-analyses of at least 5 studies, but could ultimately not be conducted due to limited material/reporting: (i) subsets according to the patient characteristics (patient chronological age, skeletal age, sex, ethnicity, craniofacial configuration, masticatory activity, jaw, baseline malocclusion severity) (ii) subsets according to the different experimental interventions (different aligner systems) or the different control interventions (type of fixed appliance) (iii) subset according to any co-interventions administered (like supplemental vibration, surgery, skeletal anchorage, extraoral traction, light therapy, pharmacological interventions etc) (iv) subsets according to the inclusion of tooth extractions in the treatment plan (v) subsets to the treatment provider, including experience each system and status (orthodontist / general dentist).

Supplementary Table 2. Literature search (as of April 7th, 2019) for each database with the corresponding hits.

Database	Search	Limits	Hits
MEDLINE	(orthodon* OR malocclusion* OR "tooth movement" OR "fixed appliances") AND (aligner* OR "clear aligner" OR "clear aligners" OR "ClearCorrect" OR "Invisalign" OR "Orthocaps" OR "TwinAligner")		392
Embase	Same as MEDLINE		60
CDSR	Same as MEDLINE		1
DARE	Same as MEDLINE		0
CENTRAL	Same as MEDLINE		41
Scopus	Same as MEDLINE	Dentistry	260
WOK	Same as MEDLINE	DENTISTRY ORAL SURGERY MEDICINE	200
VHL	Same as MEDLINE		422
Total			**1376**

CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Cochrane Database of Abstracts of Reviews of Effects; VHL, Virtual Health Library; WOK, Web of Knowledge.

Supplementary Table 2. Communications with authors of identified studies, including reason and status.

Nr	Paper	Reason	Status
1	Fetouh O. Comparison of treatment outcome of Invisalign® and traditional fixed orthodontics by model analysis using ABO Objective Grading System. State University of New York at Buffalo, 2009.	Fulltext / confounder adjustment	Sent at Dr. Fetouh on 12.04.19; ordered-received from Uni-Zurich on 06.05.19; sent reminder 16.07.2019
2	Preston KA. Treatment and Post-treatment Posterior Occlusal Changes in Invisalign® and Traditional Braces: A Randomized Controlled. MSc Thesis, Texas A & M University, 2017.	Fulltext	Sent at Dr. Preston on 12.04; Uni-Zurich says it is under embargo.
3	林佳强;周昱;;隐形矫治器和传统金属矫治器的疗效比较[J];广东微量元素科学;2014年08期 / Lin J, Zhou Y. [Assessment of Invisalign Treatment Outcomes Compared with Braces by Using the ABO Model Grading System]. Guangdong Trace Elements Science 2014-08	Fulltext / matching	Obtained through Uni-Zurich; sent to Dr. Lin & Dr. Zhou to ask for matching on 06.05.2019; sent reminder 16.07.2019
4	王冠, 杨璐, 张玉峰, 罗三莲, 郑纪伟. 无托槽隐形矫治器和直丝弓矫治器对切牙牙根吸收的影响. 上海口腔医学 2017, Vol. 26 Issue (1): 121-124. / Wang G, Yang L, Zhang YF, Luo SL, Zheng JW. [A retrospective study on incisor root resorption in patients treated with bracketless invisible appliance and straight wire appliance]. Shanghai Kou Qiang Yi Xue. 2017 Feb;26(1):121-124.	Fulltext / confounder adjustment	Sent at Dr. Wang on 12.04; obtained through Uni-Zurich on 06.05.19; sent reminder 16.07.2019
5	Buschang PH, Shaw SG, Ross M, Crosby D, Campbell PM. Comparative time efficiency of aligner therapy and conventional edgewise braces. Angle Orthod. 2014;84(3):391-6.	Matching?	Sent at Dr. Buschang on 12.04
6	Cooper-Kazaz R, Ivgi I, Canetti L, Bachar E, Tsur B, Chaushu S, et al. The impact of personality on adult patients' adjustability to orthodontic appliances. Angle Orthod. 2013;83(1):76-82.	Matching?	Sent at Dr. Shalish on 12.04
7	Eissa O, Carlyle T, El-Bialy T. Evaluation of root length following treatment with clear aligners and two different fixed orthodontic appliances. A pilot study. J Orthod Sci. 2018;7:11.	Matching?	Sent at Dr. Eissa on 12.04
8	Farronato G, Re D, Augusti G, Butti A, Augusti D. Biomimetic orthodontic treatments: Preferences of adult patients and analysis of the Willingness-To-Pay index. Dental Cadmos. 2016;84(7):408-17.	Matching?	Sent at Dr. Augusti on 12.04
9	Flores-Mir C, Brandelli J, Pacheco-Pereira C. Patient satisfaction and quality of life status after 2 treatment modalities: Invisalign and conventional fixed appliances. Am J Orthod Dentofacial Orthop. 2018;154(5):639-44.	Matching?	Sent at Dr. Pacheco-Pereira on 12.04
10	Fowler B. A comparison of root resorption between Invisalign treatment and contemporary orthodontic treatment. University of Southern California, ProQuest Dissertations Publishing, 2010.	Matching?	Sent at Dr. Fowler on 12.04
11	Garnett BS, Mahood K, Nguyen M, Al-Khateeb A, Liu S, Boyd R, et al. Cephalometric comparison of adult anterior open bite treatment using clear aligners and fixed appliances. Angle Orthod. 2019;89(1):3-9.	Matching?	Sent at Dr. Oh on 12.04; responded 05.05.19: no matching variables measured
12	Grunheid T, Gaalaas S, Hamdan H, Larson BE. Effect of clear aligner therapy on the buccolingual inclination of mandibular canines and the intercanine distance. Angle Orthod. 2016;86(1):10-6.	Matching?	Sent at Dr. Grunheid on 12.04
13	Han JY. A comparative study of combined periodontal and orthodontic treatment with fixed appliances and clear aligners in patients with periodontitis. J Periodontal Implant Sci. 2015;45(6):193-204.	Matching?	Sent at Dr. Han on 12.04; answered on 16.04 and sent raw data.
14	Hussin A. Comparison of White Spot Lesions among Clear Aligners, Self-Ligating Brackets and Conventional Brackets - A Randomized Controlled Clinical Trial. MSc Thesis, University of Connecticut, 2017.	Matching?	No e-mail address found
15	Iglesias-Linares A, Sonnenberg B, Solano B, Yanez-Vico RM, Solano E, Lindauer SJ, et al. Orthodontically induced external apical root resorption in patients treated with fixed appliances vs removable aligners. Angle Orthod. 2017;87(1):3-10.	Matching?	Sent at Dr. Iglesias-Linares on 12.04; replied 21.04.19: asked what data are needed; sent reminder 16.07.2019
16	Kuncio D, Maganzini A, Shelton C, Freeman K. Invisalign and traditional orthodontic treatment postretention outcomes compared using the American Board of Orthodontics objective grading system. Angle Orthod. 2007;77(5):864-9.	Matching?	Sent at Dr. Kuncio on 12.04; sent reminder 16.07.2019
17	Pavoni C, Lione R, Lagana G, Cozza P. Self-ligating versus Invisalign: analysis of dento-alveolar effects. Ann Stomatol (Roma). 2011;2(1-2):23-7.	Matching?	Sent at Dr. Lagana on 12.04
18	Sfondrini MF, Gandini P, Castroflorio T, Garino F, Mergati L, D'Anca K, et al. Buccolingual Inclination Control of Upper Central Incisors of Aligners: A Comparison with Conventional and Self-Ligating Brackets. Biomed Res Int. 2018;2018:9341821.	Matching?	Sent at Dr. Scribante on 12.04; answered 17.04.2019 that will search for the data; sent reminder 16.07.2019
19	Djeu G, Shelton C, Maganzini A. Outcome assessment of Invisalign and traditional orthodontic treatment compared with the American Board of Orthodontics objective grading system. Am J Orthod Dentofacial Orthop. 2005;128(3):292-8; discussion 8.	Confounder adjustment	Sent at Dr. Djeu on 12.04; answered 12.04--only measured crowding for severity; sent reminder 16.07.2019
20	Gu J, Tang JS, Skulski B, Fields HW, Jr., Beck FM, Firestone AR, et al. Evaluation of Invisalign treatment effectiveness and efficiency compared with conventional fixed appliances using the Peer Assessment Rating index. Am J Orthod Dentofacial Orthop. 2017;151(2):259-66.	Confounder adjustment	Sent at Dr. Deguchi on 12.04; sent reminder 16.07.2019
21	Hennessy J, Garvey T, Al-Awadhi EA. A randomized clinical trial comparing mandibular incisor proclination produced by fixed labial appliances and clear aligners. Angle Orthod. 2016;86(5):706-12.	Confounder adjustment	Sent at Dr. Hennessy on 12.04; sent reminder 16.07.2019
22	Lanteri V, Farronato G, Lanteri C, Caravita R, Cossellu G. The efficacy of orthodontic treatments for anterior crowding with Invisalign compared with fixed appliances using the Peer Assessment Rating Index. Quintessence Int. 2018;49(7):581-7.	Confounder adjustment	Sent at Dr. Cossellu on 12.04; answered 12.04--will try to look up for the data; sent reminder 16.07.2019
		Missing SDs / additional data	Sent at Dr. Cossellu on 10.07
23	Li W, Wang S, Zhang Y. The effectiveness of the Invisalign appliance in extraction cases using the the ABO model grading system: a multicenter randomized controlled trial. Int J Clin Exp Med. 2015;8(5):8276-82.	Confounder adjustment	Sent at Dr. Zhang on 12.04; sent reminder 16.07.2019

24	Robitaille P. Traitement combiné d'orthodontie et de chirurgie orthognatique avec Invisalign® : revue de la durée de traitement et des résultats obtenus. MSc Thesis University of Montreal, 2016.	Confounder adjustment	Sent at Dr. Robitaille on 12.04; sent reminder 16.07.2019
25	Yi J, Xiao J, Li Y, Li X, Zhao Z. External apical root resorption in non-extraction cases after clear aligner therapy or fixed orthodontic treatment. J Dent Sci. 2018;13(1):48-53.	Confounder adjustment	Sent at Dr. Li on 12.04; sent reminder 16.07.2019
26	Abbate GM, Caria MP, Montanari P, Mannu C, Orru G, Caprioglio A, et al. Periodontal health in teenagers treated with removable aligners and fixed orthodontic appliances. J Orofac Orthop. 2015;76(3):240-50	Missing SDs	Sent at Dr. Abbate on 10.07

Supplementary Table 3. List of studies identified from the literature search and their inclusion/exclusion status with reasons.

Nr	Paper	Status
1	[No authors] Erratum: Impacts of fixed orthodontic appliance and clear-aligner on daily performance in adult patients with moderate need for treatment (Patient Preference and Adherence, (2016) 10, (1639-1645)). Patient Preference and Adherence. 2016;10:2321.	Excluded by title
2	[No authors] Impacts of fixed orthodontic appliance and clear-aligner on daily performance in adult patients with moderate need for treatment [Retraction]. Patient Prefer Adherence. 2016;10:2321.	Excluded by title
3	Agarwal M, Wible E, Ramir T, Altun S, Viana G, Evans C, et al. Long-term effects of seven cleaning methods on light transmittance, surface roughness, and flexural modulus of polyurethane retainer material. Angle Orthod. 2018;88(3):355-62.	Excluded by title
4	Al-Hamlan N, Al-Ruwaithi MM, Al-Shraim N, El-Metwaaly A. Motivations and future practice plans of orthodontic residents in Saudi Arabia. J Orthod Sci. 2013;2(2):67-72.	Excluded by title
5	Aljabaa A, Almoammar K, Aldrees A, Huang G. Effects of vibrational devices on orthodontic tooth movement: A systematic review. Am J Orthod Dentofacial Orthop. 2018;154(6):768-79.	Excluded by title
6	Arun M, Usman Q, Johal A. Orthodontic treatment modalities: a qualitative assessment of Internet information. J Orthod. 2017;44(2):82-9.	Excluded by title
7	Aulakh R. The Anterior Ratio: The Missing Link between Orthodontics and Aesthetic Dentistry. Case Rep Dent. 2013;2013:470637.	Excluded by title
8	Baysal A, Uysal T, Gul N, Alan MB, Ramoglu SI. Comparison of three different orthodontic wires for bonded lingual retainer fabrication. Korean J Orthod. 2012;42(1):39-46.	Excluded by title
9	Ben Mohimd H, Bahije L, Zaoui F, Halimi A, Benyahia H. Is systematic mandibular retention mandatory? A systematic review. Int Orthod. 2018;16(1):114-32.	Excluded by title
10	Blazejewski SW, 3rd. Thermoplastic inclined plane aligner for correction of bilateral mandibular canine tooth distoclusion in a cat. J Vet Dent. 2013;30(4):236-47.	Excluded by title
11	Bressler JM, Hamamoto S, King GJ, Bollen AM. Chapter 11: Invisalign Therapy-A Systematic Review of Lower Quality Evidence. Evidence-Based Orthodontics2011. p. 167-80.	Excluded by title
12	Brezniak N, Birnboim-Blau G, Bar-Hama P, Zoizner R, Dinbar A, Wasserstein A. [The inaccuracy of the panoramic radiograph as a tool to determine tooth inclination]. Refuat Hapeh Vehashinayim (1993). 2012;29(1):36-9, 65.	Excluded by title
13	Burk T, Orellana M. Assessment of graduate orthodontic programs in North America. J Dent Educ. 2013;77(4):463-75.	Excluded by title
14	Cai YQ, Yang XX, He BW, Yao J. Finite element method analysis of the periodontal ligament in mandibular canine movement with transparent tooth correction treatment. Bmc Oral Health. 2015;15.	Excluded by title
15	Cassetta M, Pranno N, Stasolla A, Orsogna N, Fierro D, Cavallini C, et al. The effects of a common stainless steel orthodontic bracket on the diagnostic quality of cranial and cervical 3T- MR images: a prospective, case-control study. Dentomaxillofac Radiol. 2017;46(6):20170051.	Excluded by title
16	Comba B, Parrini S, Rossini G, Castroflorio T, Deregibus A. A Three-Dimensional Finite Element Analysis of Upper-Canine Distalization with Clear Aligners, Composite Attachments, and Class II Elastics. J Clin Orthod. 2017;51(1):24-8.	Excluded by title
17	Ellis D. Letter about Invisalign practices--important! J Okla Dent Assoc. 2012;103(1):26.	Excluded by title
18	Gomez JP, Pena FM, Martinez V, Giraldo DC, Cardona CI. Initial force systems during bodily tooth movement with plastic aligners and composite attachments: A three-dimensional finite element analysis. Angle Orthod. 2015;85(3):454-60.	Excluded by title
19	Gonner U. European College of Orthodontics: Commission of Affiliation and Titularisation. Int Orthod. 2016;14(2):245-61.	Excluded by title
20	Goto M, Yanagisawa W, Kimura H, Inou N, Maki K. A method for evaluation of the effects of attachments in aligner-type orthodontic appliance: Three-dimensional finite element analysis. Orthodontic Waves. 2017;76(4):207-14.	Excluded by title
21	Jager K. Twitter-Analysis of the Orthodontic Patient Experience with Braces vs. Invisalign. Informationen Aus Orthodontie Und Kieferorthopaedie. 2017;49(3):164-5.	Excluded by title
22	Jeremiah HG, Bister D, Newton JT. Social perceptions of adults wearing orthodontic appliances: a cross-sectional study. Eur J Orthod. 2011;33(5):476-82.	Excluded by title
23	Ko HC, Liu W, Hou D, Torkan S, Spiekerman C, Huang GJ. Recommendations for clear aligner therapy using digital or plaster study casts. Prog Orthod. 2018;19(1):22.	Excluded by title
24	Livas C, Delli K, Pandis N. "My Invisalign experience": content, metrics and comment sentiment analysis of the most popular patient testimonials on YouTube. Prog Orthod. 2018;19(1):3.	Excluded by title
25	Mackay MM, Fallah M, Danyal T. Acquisition of a Digital Intraoral Scanning Device: An Examination of Practice Volume Changes and the Economic Impact via an Interrupted Time Series Analysis. J Clin Dent. 2017;28((Suppl)):S1-5.	Excluded by title
26	Mangano F, Gandolfi A, Luongo G, Logozzo S. Intraoral scanners in dentistry: a review of the current literature. BMC Oral Health. 2017;17(1):149.	Excluded by title
27	Noll D, Mahon B, Shroff B, Carrico C, Lindauer SJ. Twitter analysis of the orthodontic patient experience with braces vs Invisalign. Angle Orthod. 2017;87(3):377-83.	Excluded by title
28	Park JM, Choi SA, Myung JY, Chun YS, Kim M. Impact of Orthodontic Brackets on the Intraoral Scan Data Accuracy. BioMed Research International. 2016;2016.	Excluded by title
29	Podobas-Muderrisoglu B, Krasny M, Zadurska M. Retention in orthodontics. Part 1: Removable retainers – A literature review. Forum Ortodontyczne. 2014;10(4):287-94.	Excluded by title
30	Prasanna MPK, Handa A, Nehra K, Sharma M. Trends in Contemporary Orthodontic Research Publications: Evaluation of Three Major Orthodontic Journals. Apos Trends in Orthodontics. 2017;7(6):287-93.	Excluded by title
31	Raghavan AS, Sathyanarayana HP, Kailasam V, Padmanabhan S. Comparative evaluation of salivary bisphenol A levels in patients wearing vacuum-formed and Hawley retainers: An in-vivo study. Am J Orthod Dentofacial Orthop 2017;151(3):471-6.	Excluded by title
32	Riolo C, Finkleman SA, Kaltschmidt C. Lingual orthodontics: Understanding the issues is the key to success with lingual mechanics. Seminars in Orthodontics. 2018;24(3):271-85.	Excluded by title
33	Roscoe MG. Reabsorção radicular inflamatória induzida ortodonticamente: revisão sistemática e análise por elementos finitos. 2015:112-.	Excluded by title
34	Schupp W, Haubrich J. Chapter 5: Advantages of the Invisalign System. Aligner Orthodontics: Diagnostics, Biomechanics, Planning and Treatment2016. p. 351-8.	Excluded by title
35	Schupp W, Haubrich J. Chapter 4: Treatment of Different Malocclusions with Aligners. Aligner Orthodontics: Diagnostics, Biomechanics, Planning and Treatment2016. p. 41-349.	Excluded by title
36	Schupp W, Haubrich J. Chapter 3: Treatment Planning and Treatment with Aligners. Aligner Orthodontics: Diagnostics, Biomechanics, Planning and Treatment2016. p. 31-40.	Excluded by title
37	Schuster G, Reichle R, Bauer RR, Schopf PM. Allergies induced by orthodontic alloys: Incidence and impact on treatment. Results of a survey in private orthodontic offices in the federal state of Hesse, Germany. J Orofac Orthop 2004;65(1):48-59.	Excluded by title
38	Sifakakis I, Zinelis S, Eliades T. Chapter 18: Aligners for orthodontic applications. Orthodontic Applications of Biomaterials: A Clinical Guide. Woodhead Publishing Series in Biomaterials2017. p. 275-85.	Excluded by title

39	Singh P. Orthodontic apps for smartphones. J Orthod. 2013;40(3):249-55.	Excluded by title
40	Sombuntham NP, Songwattana S, Atthakorn P, Jungudomjaroen S, Panyarachun B. Early tooth movement with a clear plastic appliance in rats. Am J Orthod Dentofacial Orthop. 2009;136(1):75-82.	Excluded by title
41	Tai S. Chapter 2: A Comparison between Edgewise Appliances and Clear Aligners. Clear Aligner Technique2018. p. 7-16.	Excluded by title
42	Tai S. Chapter 4: Clincheck Software Design. Clear Aligner Technique2018. p. 23-54.	Excluded by title
43	Tai S. Chapter 7: Resolution of Crowding. Clear Aligner Technique2018. p. 81-94.	Excluded by title
44	Thiesen G, do Rego MVNN, Faber J, Kim KB. An interview with Benedict Wilmes. Dental Press Journal of Orthodontics. 2016;21(6):26-33.	Excluded by title
45	Veneziani M. Ceramic laminate veneers: clinical procedures with a multidisciplinary approach. International Journal of Esthetic Dentistry. 2017;12(4):426-48.	Excluded by title
46	Yokoi Y, Arai A, Kawamura J, Uozumi T, Usui Y, Okafuji N. Effects of Attachment of Plastic Aligner in Closing of Diastema of Maxillary Dentition by Finite Element Method. J Healthc Eng. 2019;2019:1075097.	Excluded by title
47	Yu Y, Sun J, Lai W, Wu T, Koshy S, Shi Z. Interventions for managing relapse of the lower front teeth after orthodontic treatment. Cochrane Database Syst Rev. 2013(9):Cd008734.	Excluded by title
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475	Parrini S, Comba B, Rossini G, Ravera S, Cugliari G, De Giorgi I, et al. Postural changes in orthodontic patients treated with clear aligners: A rasterstereographic study. J Electromyogr Kinesiol. 2018;38:44-8.	No fixed appliances used
476	Patini R, Gallenzi P, Meuli S, Paoloni V, Cordaro M. Clear aligners' effects on aesthetics: evaluation of facial wrinkles. J Clin Exp Dent. 2018;10(7):e696-e701.	No fixed appliances used
477	Ravera S, Castroflorio T, Garino F, Daher S, Cugliari G, Deregibus A. Maxillary molar distalization with aligners in adult patients: a multicenter retrospective study. Prog Orthod. 2016;17:12.	No fixed appliances used
478	Schaefer I, Braumann B. Halitosis, oral health and quality of life during treatment with Invisalign((R)) and the effect of a low-dose chlorhexidine solution. J Orofac Orthop. 2010;71(6):430-41.	No fixed appliances used
479	Shipley TS. Effects of High Frequency Acceleration Device on Aligner Treatment-A Pilot Study. Dent J (Basel). 2018;6(3).	No fixed appliances used
480	Simon M, Keilig L, Schwarze J, Jung BA, Bourauel C. Treatment outcome and efficacy of an aligner technique--regarding incisor torque, premolar derotation and molar distalization. BMC Oral Health. 2014;14:68.	No fixed appliances used
481	Solano-Mendoza B, Sonnemberg B, Solano-Reina E, Iglesias-Linares A. How effective is the Invisalign(R) system in expansion movement with Ex30' aligners? Clin Oral Investig. 2017;21(5):1475-84.	No fixed appliances used
482	Tepedino M, Paoloni V, Cozza P, Chimenti C. Movement of anterior teeth using clear aligners: a three-dimensional, retrospective evaluation. Prog Orthod. 2018;19(1):9.	No fixed appliances used
483	Thavarajah R, Thennukonda RA. Analysis of adverse events with use of orthodontic sequential aligners as reported in the manufacturer and user facility device experience database. Indian J Dent Res. 2015;26(6):582-7.	No fixed appliances used
484	Tuncay O, Bowman SJ, Amy B, Nicozisis J. Aligner treatment in the teenage patient. J Clin Orthod. 2013;47(2):115-9; quiz 40.	No fixed appliances used
485	Tuncay OC, Bowman SJ, Nicozisis JL, Amy BD. Effectiveness of a compliance indicator for clear aligners. J Clin Orthod. 2009;43(4):263-8; quiz 73-4.	No fixed appliances used
486	Vardimon AD, Robbins D, Brosh T. In-vivo von Mises strains during Invisalign treatment. Am J Orthod Dentofacial Orthop. 2010;138(4):399-409.	No fixed appliances used
487	Zhang XJ, He L, Guo HM, Tian J, Bai YX, Li S. Integrated three-dimensional digital assessment of accuracy of anterior tooth movement using clear aligners. Korean J Orthod. 2015;45(6):275-81.	No fixed appliances used
488	Liu P, Wu G, Liu J, Jiao D, Guo J. Assessment of oral parafunctional behaviors and electromyographic activities of the masticatory muscles in young female patients with orthodontic invisalign treatment. International Journal of Clinical and Experimental Medicine. 2017;10(11):15323-8.	No fixed appliances used
489	Alansari S, Atique MI, Gomez JP, Hamidaddin M, Thirumoorthy SN, Sangsuwon C, et al. The effects of brief daily vibration on clear aligner orthodontic treatment. J World Fed Orthod 2018;7(4):134-40.	No fixed appliances used
490	Azeem M, Ul Hamid W. Incidence of white spot lesions during orthodontic clear aligner therapy. J World Fed Orthod 2017;6(3):127-30.	No fixed appliances used
491	Hansa I, Semaan SJ, Vaid NR, Ferguson DJ. Remote monitoring and “Tele-orthodontics”: Concept, scope and applications. Seminars in Orthodontics. 2018;24(4):470-81.	No fixed appliances used
492	Kassas W, Al-Jewair T, Preston CB, Tabbaa S. Assessment of invisalign treatment outcomes using the ABO model grading system. J World Fed Orthod 2013;2(2):e61-e4.	No fixed appliances used
493	Tettamanti P, Guarneri MP, Digirolamo E, Gracco A. Evaluation of dental movement with Invisalign method. Mondo Ortodontico. 2008;33(1):67-74.	No fixed appliances used
494	Tuncay OC, Keenan EJ. Observational study of movements in lateral extrusion. Seminars in Orthodontics. 2017;23(1):103-6.	No fixed appliances used
495	Cassetta M, Ivani M. The accuracy of computer-guided piezocision: a prospective clinical pilot study. International Journal of Oral and Maxillofacial Surgery. 2017;46(6):756-65.	No fixed appliances used
496	{ACTRN 12613000687796} Predictability of Increasing Tooth Velocity using Invisalign Aligners in a Group of Teenage Subjects. 2013.	No fixed appliances used
497	{Chi CI-ior-15007532} Comparing tooth movement efficacy and self-reported discomfort between two patterns of activation time per stage using Invisalign clear aligner: a randomized controlled trial. 2018.	No fixed appliances used
498	{DRKS 00013334} Evaluation of Efficiancy of the aligner therapy by 3d-analysis of the tooth movement during the treatment with removable PET-G aligners. 2018.	No fixed appliances used
499	{DRKS 00015613} ACCELERATING ALIGNER TREATMENT USING LOW-FREQUENCY VIBRATION: a SINGLE-CENTER, RANDOMISED CONTROLLED CLINICAL TRIAL. 2018.	No fixed appliances used
500	{NCT 02438280} Accelerated Tooth Movement With AcceleDent® and Aligners - a Pilot Project. 2015.	No fixed appliances used
501	{NCT 02550938} Primer Aligner Study. 2015.	No fixed appliances used
502	{NCT 02868554} Accelerated Invisalign Therapy in Conjunction With Acceledent Aura. 2016.	No fixed appliances used
503	{NCT 02954133} The Effect of OrthoPulse™ Photobiomodulation on Tooth Movement and Treatment Time When Used With Invisalign Treatment. 2016.	No fixed appliances used
504	{NCT 03421886} Assessment of the Efficacy of the Aerodentis System. 2018.	No fixed appliances used
505	Baldwin DK, King G, Ramsay DS, Huang G, Bollen AM. Activation time and material stiffness of sequential removable orthodontic appliances. Part 3: premolar extraction patients. Am J Orthod Dentofacial Orthop. 2008;133(6):837-45.	Both modalities used
506	Charalampakis O, Iliadi A, Ueno H, Oliver DR, Kim KB. Accuracy of clear aligners: A retrospective study of patients who needed refinement. Am J Orthod Dentofacial Orthop. 2018;154(1):47-54.	Previous treatment
507	Almasoud NN. Pain perception among patients treated with passive self-ligating fixed appliances and Invisalign aligners during the first week of orthodontic treatment. Korean J Orthod. 2018;48(5):326-32.	No eligible outcomes measured
508	Chhibber A, Agarwal S, Yadav S, Kuo CL, Upadhyay M. Which orthodontic appliance is best for oral hygiene? A randomized clinical trial. Am J Orthod Dentofacial Orthop. 2018;153(2):175-83.	No eligible outcomes measured

509	Srinath M, Reddy V, Reddy G, Ramyasree K, Swetha T, Sridhar M. Aligners: A Boon for the Gingival Health of Orthodontic Patients. Journal of International Oral Health. 2016;8(4):490-3.	No eligible outcomes measured
510	Fujiyama K, Honjo T, Suzuki M, Matsuoka S, Deguchi T. Analysis of pain level in cases treated with Invisalign aligner: comparison with fixed edgewise appliance therapy. Prog Orthod. 2014;15:64.	No eligible outcomes measured
511	Levrini L, Abbate GM, Migliori F, Orrù G, Sauro S, Caprioglio A. Assessment of the periodontal health status in patients undergoing orthodontic treatment with fixed or removable appliances. A microbiological and preliminary clinical study. Cumhuriyet Dental Journal. 2013;16(4):296-307.	No eligible outcomes measured
512	Levrini L, Mangano A, Montanari P, Margherini S, Caprioglio A, Abbate GM. Periodontal health status in patients treated with the Invisalign((R)) system and fixed orthodontic appliances: A 3 months clinical and microbiological evaluation. Eur J Dent. 2015;9(3):404-10.	No eligible outcomes measured
513	Miller KB, McGorray SP, Womack R, Quintero JC, Perelmuter M, Gibson J, et al. A comparison of treatment impacts between Invisalign aligner and fixed appliance therapy during the first week of treatment. Am J Orthod Dentofacial Orthop. 2007;131(3):302.e1-9.	No eligible outcomes measured
514	Miethke RR, Brauner K. A Comparison of the periodontal health of patients during treatment with the Invisalign system and with fixed lingual appliances. J Orofac Orthop. 2007;68(3):223-31.	No eligible outcomes measured
515	Miethke RR, Vogt S. A comparison of the periodontal health of patients during treatment with the Invisalign system and with fixed orthodontic appliances. J Orofac Orthop. 2005;66(3):219-29.	No eligible outcomes measured
516	Karkhanechi M, Chow D, Sipkin J, Sherman D, Boylan RJ, Norman RG, et al. Periodontal status of adult patients treated with fixed buccal appliances and removable aligners over one year of active orthodontic therapy. Angle Orthod. 2013;83(1):146-51.	No eligible outcomes measured
517	Shalish M, Cooper-Kazaz R, Ivgi I, Canetti L, Tsur B, Bachar E, et al. Adult patients' adjustability to orthodontic appliances. Part I: a comparison between Labial, Lingual, and Invisalign. Eur J Orthod. 2012;34(6):724-30.	No eligible outcomes measured
518	Sifakakis I, Papaioannou W, Papadimitriou A, Kloukos D, Papageorgiou SN, Eliades T. Salivary levels of cariogenic bacterial species during orthodontic treatment with thermoplastic aligners or fixed appliances: a prospective cohort study. Prog Orthod. 2018;19(1):25.	No eligible outcomes measured
519	White DW, Julien KC, Jacob H, Campbell PM, Buschang PH. Discomfort associated with Invisalign and traditional brackets: A randomized, prospective trial. Angle Orthod. 2017;87(6):801-8.	No eligible outcomes measured
520	林佳强;周昱;;隐形矫治器和传统金属矫治器的疗效比较[J];广东微量元素科学;2014年08期 / Lin J, Zhou Y. [Assessment of Invisalign Treatment Outcomes Compared with Braces by Using the ABO Model Grading System]. Guangdong Trace Elements Science 2014-08	Non-randomized study without matching
521	Buschang PH, Shaw SG, Ross M, Crosby D, Campbell PM. Comparative time efficiency of aligner therapy and conventional edgewise braces. Angle Orthod. 2014;84(3):391-6.	Non-randomized study without matching
522	Cooper-Kazaz R, Ivgi I, Canetti L, Bachar E, Tsur B, Chaushu S, et al. The impact of personality on adult patients' adjustability to orthodontic appliances. Angle Orthod. 2013;83(1):76-82.	Non-randomized study without matching
523	Eissa O, Carlyle T, El-Bialy T. Evaluation of root length following treatment with clear aligners and two different fixed orthodontic appliances. A pilot study. J Orthod Sci. 2018;7:11.	Non-randomized study without matching
524	Farronato G, Re D, Augusti G, Butti A, Augusti D. Biomimetic orthodontic treatments: Preferences of adult patients and analysis of the Willingness-To-Pay index. Dental Cadmos. 2016;84(7):408-17.	Non-randomized study without matching
525	Flores-Mir C, Brandelli J, Pacheco-Pereira C. Patient satisfaction and quality of life status after 2 treatment modalities: Invisalign and conventional fixed appliances. Am J Orthod Dentofacial Orthop. 2018;154(5):639-44.	Non-randomized study without matching
526	王冠, 杨璐, 张玉峰, 罗三莲, 郑纪伟. 无托槽隐形矫治器和直丝弓矫治器对切牙牙根吸收的影响. 上海口腔医学 2017, Vol. 26 Issue (1): 121-124. / Wang G, Yang L, Zhang YF, Luo SL, Zheng JW. [A retrospective study on incisor root resorption in patients treated with bracketless invisible appliance and straight wire appliance]. Shanghai Kou Qiang Yi Xue. 2017 Feb;26(1):121-124.	Non-randomized study without matching
527	Fowler B. A comparison of root resorption between Invisalign treatment and contemporary orthodontic treatment. University of Southern California, ProQuest Dissertations Publishing, 2010.	Non-randomized study without matching
528	Garnett BS, Mahood K, Nguyen M, Al-Khateeb A, Liu S, Boyd R, et al. Cephalometric comparison of adult anterior open bite treatment using clear aligners and fixed appliances. Angle Orthod. 2019;89(1):3-9.	Non-randomized study without matching
529	Grunheid T, Gaalaas S, Hamdan H, Larson BE. Effect of clear aligner therapy on the buccolingual inclination of mandibular canines and the intercanine distance. Angle Orthod. 2016;86(1):10-6.	Non-randomized study without matching
530	Hussin A. Comparison of White Spot Lesions among Clear Aligners, Self-Ligating Brackets and Conventional Brackets - A Randomized Controlled Clinical Trial. MSc Thesis, University of Connecticut, 2017.	Non-randomized study without matching
531	Iglesias-Linares A, Sonnenberg B, Solano B, Yanez-Vico RM, Solano E, Lindauer SJ, et al. Orthodontically induced external apical root resorption in patients treated with fixed appliances vs removable aligners. Angle Orthod. 2017;87(1):3-10.	Non-randomized study without matching
532	Kuncio D, Maganzini A, Shelton C, Freeman K. Invisalign and traditional orthodontic treatment postretention outcomes compared using the American Board of Orthodontics objective grading system. Angle Orthod. 2007;77(5):864-9.	Non-randomized study without matching
533	Pavoni C, Lione R, Lagana G, Cozza P. Self-ligating versus Invisalign: analysis of dento-alveolar effects. Ann Stomatol (Roma). 2011;2(1-2):23-7.	Non-randomized study without matching

534	Sfondrini MF, Gandini P, Castroflorio T, Garino F, Mergati L, D'Anca K, et al. Buccolingual Inclination Control of Upper Central Incisors of Aligners: A Comparison with Conventional and Self-Ligating Brackets. Biomed Res Int. 2018;2018:9341821.	Non-randomized study without matching
535	Abbate GM, Caria MP, Montanari P, Mannu C, Orru G, Caprioglio A, et al. Periodontal health in teenagers treated with removable aligners and fixed orthodontic appliances. J Orofac Orthop. 2015;76(3):240-50.	Included
536	Djeu G, Shelton C, Maganzini A. Outcome assessment of Invisalign and traditional orthodontic treatment compared with the American Board of Orthodontics objective grading system. Am J Orthod Dentofacial Orthop. 2005;128(3):292-8; discussion 8.	Included
537	Gu J, Tang JS, Skulski B, Fields HW, Jr., Beck FM, Firestone AR, et al. Evaluation of Invisalign treatment effectiveness and efficiency compared with conventional fixed appliances using the Peer Assessment Rating index. Am J Orthod Dentofacial Orthop. 2017;151(2):259-66.	Included
538	Hennessy J, Garvey T, Al-Awadhi EA. A randomized clinical trial comparing mandibular incisor proclination produced by fixed labial appliances and clear aligners. Angle Orthod. 2016;86(5):706-12.	Included
539	Han JY. A comparative study of combined periodontal and orthodontic treatment with fixed appliances and clear aligners in patients with periodontitis. J Periodontal Implant Sci. 2015;45(6):193-204.	Included; matching done
540	Lanteri V, Farronato G, Lanteri C, Caravita R, Cossellu G. The efficacy of orthodontic treatments for anterior crowding with Invisalign compared with fixed appliances using the Peer Assessment Rating Index. Quintessence Int. 2018;49(7):581-7.	Included
541	Li W, Wang S, Zhang Y. The effectiveness of the Invisalign appliance in extraction cases using the the ABO model grading system: a multicenter randomized controlled trial. Int J Clin Exp Med. 2015;8(5):8276-82.	Included
542	Fetouh O. Comparison of treatment outcome of Invisalign® and traditional fixed orthodontics by model analysis using ABO Objective Grading System. State University of New York at Buffalo, 2009.	Included
543	Preston KA. Treatment and Post-treatment Posterior Occlusal Changes in Invisalign® and Traditional Braces: A Randomized Controlled. MSc Thesis, Texas A & M University, 2017.	Included
544	Robitaille P. Traitement combiné d'orthodontie et de chirurgie orthognatique avec Invisalign® : revue de la durée de traitement et des résultats obtenus. MSc Thesis University of Montreal, 2016.	Included
545	Yi J, Xiao J, Li Y, Li X, Zhao Z. External apical root resorption in non-extraction cases after clear aligner therapy or fixed orthodontic treatment. J Dent Sci. 2018;13(1):48-53.	Included

Supplementary Table 4. Detailed assessment of included randomized trials with the RoB 2.0 tool (supplement to Table 2a).

Domain	Reference	Abbate 2015	Hennessy 2016	Li 2015	Preston 2017
1. Randomization process	**1.1**	NI	PY	Y	PY
	1.2	PY	Y	Y	NI
	1.3	Y	N	N	PN
	Assessor's Judgement	Some concerns	Low	Low	Low
2. Deviations from intended interventions	**2.1**	Y	Y	Y	Y
	2.2	Y	Y	Y	Y
	2.3	PN	PY	N	PN
	2.4	PN	PN	NA	NA
	2.5	Y	Y	NA	NA
	2.6	N	N	Y	Y
	2.7	PY	PY	NA	NA
	Assessor's Judgement	High	High	Low	Low
3. Mising outcome data	**3.1**	PY	PN	Y	Y
	3.2	NA	PN	NA	NA
	3.3	NA	PY	NA	NA
	3.4	NA	PY	NA	NA
	Assessor's judgement	Low	High	Low	Low
4. Measurement of the outcome	**4.1**	N	PN	N	N
	4.2	PN	NI	PN	PN
	4.3	Y	Y	N	N
	4.4	PY	Y	NA	NA
	4.5	PY	PY	NA	NA
	Assessor's Judgement	High	High	Low	Low
5. Selection of the reported result	**5.1**	NI	NI	NI	NI
	5.2	PN	PN	N	N
	5.3	NI	PN	NI	NI
	Assessor's Judgement	Some concerns	Some concerns	Some concerns	Some concerns
Overall	**Assessor's Judgement**	High	High	Some concerns	Some concerns
	General Note	Additionally, incomplete reporting is seen for all continous outcomes	Also, incomplete reporting of treatment duration.	Incomplete reporting for treatment duration, due to missing SDs, but these were provided by the authors after contacting them.	-

SD, standard deviation.

Supplementary Table5. Detailed assessment of included non-randomized studies with the ROBINS-I tool (supplement to Table 2b).

Domain	Reference	Djeu 2005	Fetouh 2008	Gu 2017	Han 2015	Lanteri 2018	Robitaille 2016	Yi 2018
1. Confounding	**1.1**	PY	PY	PY	PY	PY	PY	PY
	1.2	PN	PN	PN	PN	PN	PN	PN
	1.3	N	N	N	N	N	N	N
	1.4	PN	PN	PY	PN	PN	PN	PN
	1.5	NA	NA	Y	NA	NA	NA	NA
	1.6	N	N	N	N	N	N	N
	1.7	N	N	PY	N	N	N	N
	1.8	NA	NA	PY	NA	NA	NA	NA
	Judgement	Serious	Serious	Moderate	Serious	Serious	Serious	Serious
2. Selection of participants into the study	**2.1**	NI	NI	PY	NI	NI	NI	NI
	2.2	NA	NA	Y	NA	NA	NA	NA
	2.3	NA	NA	Y	NA	NA	NA	NA
	2.4	NI	NI	Y	PY	NI	NI	NI
	2.5	NA	NA	NA	NA	NA	NA	NA
	Judgement	NI	NI	Critical	NI	NI	NI	NI
3. Classification of interventions	**3.1**	Y	Y	Y	Y	Y	Y	Y
	3.2	Y	Y	Y	Y	Y	Y	Y
	3.3	N	N	N	N	N	N	N
	Judgement	Low	Low	Low	Low	Low	Low	Low
4. Deviations from intended interventions	**4.1**	NI	NI	NI	NI	NI	NI	NI
	4.2	NA	NA	NA	NA	NA	NA	NA
	4.3	NI	NI	NI	NI	Y	NI	NI
	4.4	PY	NI	PY	PY	Y	NI	NI
	4.5	NI	NI	NI	NI	PY	NI	NI
	4.6	NA	NA	NA	NA	NA	NA	NI
	Judgement	NI	NI	NI	NI	Low	NI	NI
5. Missing data	**5.1**	PY	PY	PY	PY	PY	PY	PY
	5.2	PN	PN	PN	PN	PN	PN	PN
	5.3	NI	NI	NI	NI	NI	NI	NI
	5.4	NA	NA	NA	NA	NA	NA	NA
	5.5	NA	NA	NA	NA	NA	NA	NA
	Judgement	NI	NI	NI	NI	NI	NI	NI
6. Measurement of outcomes	**6.1**	PY	PY	PY	PY	PY	PY	PY
	6.2	PY	PY	PN	PN	PY	PY	PN
	6.3	PY	PY	PY	PY	PY	PY	PY
	6.4	PN	PN	PN	PN	PN	PN	PN
	Judgement	Moderate	Moderate	Low	Low	Moderate	Moderate	Low
7. Selection of the reported result	**7.1**	PN	PN	PN	PN	PN	PN	PN
	7.2	PN	PN	PN	PN	PN	PN	PN
	7.3	PN	PN	PN	PN	PN	PN	PY
	Judgement	Low	Low	Low	Low	Low	Low	Moderate
Overall	**Judgement**	Serious	Serious	Critical	Serious	Serious	Serious	Serious

N, no; NA, not applicable; NI, no information; PN, probably not; PY, probably yes; Y, yes.

Supplementary Table 6. Results of the Han 2015 study with both in the originally-reported sample and the 'matched' sub-sample extracted from the study to include in this review.

		Original sample				'Matched' sample			
		FX	**AL**	**P value***		**FX**	**AL**	**P value***	**P value†**
	Patients	19	16			9	10		
	Age – mean (SD)	51.8 (7.4)	54.4 (11.4)	0.43		47.3 (6.1)	51.2 (8.8)	0.29	
Jaw	Maxilla – n (%)	8 (42%)	5 (31%)	0.51		4 (44%)	3 (30%)	0.65	
	Mandible – n (%)	11 (58%)	11 (69%)			5 (56%)	7 (70%)		
	DI – mean (SD)	4.9 (1.4)	4.1 (1.5)	0.08		4.3 (1.2)	4.5 (1.6)	0.81	
Type of irregularity	Crowding – n (%)	10 (53%)	11 (69%)	0.56		8 (89%)	9 (90%)	1.00	
	Spacing – n (%)	2 (11%)	2 (13%)			0 (0%)	0 (0%)		
	Pathologic migration – n (%)	7 (37%)	3 (19%)			1 (11%)	1 (10%)		
Severity of irregularity	Grade 1 – n (%)	0 (0%)	0 (0%)	0.74		0 (0%)	0 (0%)	1.00	
	Grade 2 – n (%)	2 (11%	2 (13%)			1 (11%)	1 (10%)		
	Grade 3 – n (%)	6 (32%)	7 (44%)			5 (56%)	5 (50%)		
	Grade 4 – n (%)	7 (37%)	6 (38%)			3 (33%)	3 (30%)		
	Grade 5 – n (%)	4 (21%)	1 (6%)			0 (0%)	1 (10%)		
	Tx duration – mean (SD)	4.2 (1.7)	6.0 (2.3)	0.01		3.9 (1.1)	6.0 (2.3)	0.03	
	PD Pre-Tx – mean (SD)	3.0 (0.8)	2.1 (0.4)	<0.001		2.4 (0.4)	2.3 (0.4)	0.50	
	PD Post-Tx – mean (SD)	2.6 (0.1)	2.6 (0)	0.37		2.6 (0)	2.6 (0)	1.00	0.38
	PD reduction – mean (SD)	0.5 (0.3)	0.2 (0.3)	0.01		0.4 (0.3)	0.3 (0.3)	0.28	
	ABL Pre-Tx – mean (SD)	4.0 (1.5)	2.9 (0.6)	0.01		2.9 (1.1)	3.0 (0.5)	0.92	
	ABL Post-Tx – mean (SD)	3.5 (1.1)	2.7 (0.5)	0.02		2.6 (0.5)	2.7 (0.6)	0.82	0.75
	ABL reduction – mean (SD)	0.5 (0.7)	0.2 (0.5)	0.13		0.3 (0.8)	0.3 (0.4)	0.94	

* p value from t-test (for continuous outcomes) and chi-square / Fisher's exact test (for binary outcomes).

† p value from regression model on the post-treatment value with pre-treatment values as covariate.

ABL, alveolar bone level; DI, discrepancy index; FX, fixed appliance; AL, aligner; SD, standard deviation; Tx, treatment; BL, bone level; PPD, periodontal probing depth.

Supplementary Table 7. Results of all outcomes reported from all included studies.

id	study	out	Effect (95%C I)	P	SD	Rel
1	Abbate 2015	PPD change (incisors; 3 months)	MD:-0.66 (-0.92,-0.40)	<0.001	0.51	Yes
2	Abbate 2015	PPD change (incisors; 6 months)	MD:-0.87 (-1.14,-0.60)	<0.001	0.61	Yes
3	Abbate 2015	PPD change (incisors; 12 months)	MD:-0.77 (-1.03,-0.51)	<0.001	0.45	Yes
4	Abbate 2015	PPD change (molars; 3 months)	MD:-0.60 (-0.87,-0.33)	<0.001	0.44	Yes
5	Abbate 2015	PPD change (molars; 6 months)	MD:-0.84 (-1.15,-0.53)	<0.001	0.59	Yes
6	Abbate 2015	PPD change (molars; 12 months)	MD:-1.07 (-1.41,-0.74)	<0.001	0.70	Yes
7	Djeu 2005	ABO-OGS component 1: alignment	MD:1.06 (-0.27,2.39)	0.12		-
8	Djeu 2005	ABO-OGS component 2: marginal ridges	MD:0.46 (-0.56,1.48)	0.38		-
9	Djeu 2005	ABO-OGS component 3: buccolingual inclination	MD:1.38 (0.31,2.45)	0.01	2.63	No
10	Djeu 2005	ABO-OGS component 4: occlusal contacts	MD:4.81 (2.42,7.20)	<0.001	4.66	Yes
11	Djeu 2005	ABO-OGS component 5: occlusal relationship	MD:2.21 (0.32,4.10)	0.02	4.71	No
12	Djeu 2005	ABO-OGS component 6: overjet	MD:2.65 (1.15,4.15)	0.001	2.54	Yes
13	Djeu 2005	ABO-OGS component 7: interproximal contacts	MD:0.12 (-0.48,0.72)	0.70		-
14	Djeu 2005	ABO-OGS component 8: root angulation	MD:0.71 (-0.14,1.56)	0.10		-
15	Djeu 2005	ABO-OGS total score	MD:13.14 (7.63,18.65)	<0.001	11.73	Yes
16	Djeu 2005	ABO-OGS failure (score>30)	RR:1.52 (1.12,2.07)	0.008	0.00	No
17	Djeu 2005	Treatment duration (months)	MD:-3.60 (-6.42,-0.78)	0.01		??
18	Fetouh 2008	ABO-OGS component 1: alignment	MD:1.55 (-0.03,3.13)	0.05	3.06	No
19	Fetouh 2008	ABO-OGS component 2: marginal ridges	MD:-1.77 (-2.74,-0.80)	<0.001	2.57	No
20	Fetouh 2008	ABO-OGS component 3: buccolingual inclination	MD:-1.24 (-1.96,-0.52)	0.001	1.95	No
21	Fetouh 2008	ABO-OGS component 4: occlusal contacts	MD:-3.04 (-4.48,-1.60)	<0.001	3.20	No
22	Fetouh 2008	ABO-OGS component 5: occlusal relationship	MD:0.73 (-0.43,1.89)	0.22		-
23	Fetouh 2008	ABO-OGS component 6: overjet	MD:-2.56 (-3.88,-1.24)	<0.001	2.84	No
24	Fetouh 2008	ABO-OGS component 7: interproximal contacts	MD:0	-		-
25	Fetouh 2008	ABO-OGS total score (7/8 components)	MD:-6.35 (-9.40,-3.30)	<0.001	5.75	Yes
26	Gu 2017	Treatment duration (months)	MD:-5.73 (-8.69,-2.77)	<0.001	5.92	No
27	Gu 2017	PAR reduction	MD:-3.37 (-6.35,-0.39)	0.03	8.06	No
28	Gu 2017	PAR reduction per month	MD:0.39 (0.09,0.69)	0.01	0.69	No
29	Gu 2017	PAR component 1: upper anteriors	MD:-1.00 (-1.86,-0.14)	0.02	2.21	No
30	Gu 2017	PAR component 2: lower anteriors	MD:-0.4 (-1.42,0.53)	0.38		-
31	Gu 2017	PAR component 3: anteroposterior relationship	MD:-0.33 (-0.84,0.18)	0.20		-
32	Gu 2017	PAR component 4: transverse relationship	MD:-0.17 (-0.42,0.08)	0.18		-
33	Gu 2017	PAR component 5: vertical relationship	MD:0.04 (-0.02,0.10)	0.16		-
34	Gu 2017	PAR component 6: overjet	MD:0.12 (-2.12,2.36)	0.92		-
35	Gu 2017	PAR component 7: overbite	MD:-1.03 (-1.90,-0.16)	0.02	2.53	No
36	Gu 2017	PAR component 8: midline deviation	MD:-0.58 (-1.34,0.18)	0.14		-
37	Gu 2017	PAR improvement (reduction>22)	NC			-
38	Gu 2017	PAR great improvement (reduction>30)	RR:0.50 (0.27,0.91)	0.02	0.00	Yes
39	Han 2015	Alignment duration (months)	MD:2.10 (0.50,3.70)	0.01	1.10	Yes
40	Han 2015	Periodontal probing depth post-treatment	MD:0 (-0.36,0.36)	1.00		-
41	Han 2015	Alveolar bone level post-treatment	MD:0.10 (-0.40,0.60)	0.69		-
42	Han 2015	Periodontal probing depth reduction	MD:-0.10 (-0.37,0.17)	0.47		-
43	Han 2015	Alveolar bone level reduction	MD:0 (-0.58,0.58)	1.00		-
44	Hennessy 2016	Lower incisor inclination to mandibular plane	MD:-1.90 (-4.14,0.34)	0.10		-
45	Hennessy 2016	Treatment duration (months)	MD:-1.10 (-2.28,0.08)	0.07		-
46	Lanteri 2018	Treatment duration (months)	MD:2.00 (0.61,3.39)	<0.001	4.00	No
47	Lanteri 2018	PAR post-treatment	MD:-1.00 (-1.98,-0.02)	0.05	4.00	No
48	Lanteri 2018	PAR reduction	MD:-0.50 (-2.21,1.21)	0.57		-
49	Lanteri 2018	PAR great improvement (reduction>30)	RR:0.91 (0.67,1.25)	0.57		-
50	Lanteri 2018	Maxillary alignment not perfect	NC	-	0.00	-
51	Lanteri 2018	Mandibular alignment not perfect	RR:0.67 (0.29,1.56)	0.35		-
52	Lanteri 2018	Gingival recession	RR:0.90 (0.31,2.68)	0.86		
53	Li 2015	ABO-OGS component 1: alignment	MD:-0.38 (-1.55,0.79)	0.52		-
54	Li 2015	ABO-OGS component 2: marginal ridges	MD:0.25 (-0.76,1.26)	0.63		-
55	Li 2015	ABO-OGS component 3: buccolingual inclination	MD:0.73 (0.39,1.07)	<0.00	1.13	No
56	Li 2015	ABO-OGS component 4: occlusal contacts	MD:0.93 (-0.28,2.14)	0.13		-
57	Li 2015	ABO-OGS component 5: occlusal relationship	MD:0.95 (0.52,1.38)	<0.001	1.23	No

58	Li 2015	ABO-OGS component 6: overjet	MD:1.15 (0.49,1.81)	0.001	1.23	No
59	Li 2015	ABO-OGS component 7: interproximal contacts	MD:0.05 (-1.26,1.36)	0.94		-
60	Li 2015	ABO-OGS component 8: root angulation	MD:0.70 (0.25,1.15)	0.002	1.25	No
61	Li 2015	ABO-OGS total score	MD:4.38 (2.20,6.57)	<0.001	6.24	No
62	Li 2015	ABO-OGS failure (score>30)	RR:1.33 (0.81,2.20)	0.26		-
63	Li 2015	Treatment duration (months)	NC			-
64	Preston 2017	Treatment duration (months)	MD:6.72 (3.78,9.66)	<0.001	4.68	Yes
65	Preston 2017	ABO-OGS component 2: marginal ridges	NC			-
66	Preston 2017	ABO-OGS component 3: buccolingual inclination	NC			-
67	Robitaille 2016	ABO-OGS component 1: alignment	MD:4.21 (2.61,5.81)	<0.001	1.50	Yes
68	Robitaille 2016	ABO-OGS component 2: marginal ridges	MD:0.87 (-0.53,2.27)	0.22		-
69	Robitaille 2016	ABO-OGS component 3: buccolingual inclination	MD:0.42 (-1.43,2.27)	0.66		-
70	Robitaille 2016	ABO-OGS component 4: occlusal contacts	MD:4.06 (1.56,6.56)	0.001	3.49	Yes
71	Robitaille 2016	ABO-OGS component 5: occlusal relationship	MD:0.67 (-1.06,2.40)	0.45		-
72	Robitaille 2016	ABO-OGS component 6: overjet	MD:2.47 (-0.35,5.29)	0.09		-
73	Robitaille 2016	ABO-OGS component 7: interproximal contacts	MD:0.01 (-0.18,0.20)	0.92		-
74	Robitaille 2016	ABO-OGS component 8: root angulation	MD:0.92 (0.44,1.40)	<0.001	0.47	Yes
75	Robitaille 2016	ABO-OGS total score	MD:13.63 (8.03,19.23)	<0.001	6.01	Yes
76	Robitaille 2016	ABO-OGS failure (score>30)	RR:1.98 (1.17,3.34)	0.01	0.00	No
77	Robitaille 2016	Treatment duration – pre-surgery (months)	MD:-7.38 (-11.00,-3.76)	<0.001	7.87	No
78	Robitaille 2016	Treatment duration – post-surgery (months)	MD:2.71 (-1.56,6.98)	0.21		-
79	Robitaille 2016	Treatment duration – total (months)	MD:-4.86 (-10.72,1.00)	0.10		-
80	Yi 2018	Treatment duration (months)	MD:1.25 (-0.90,3.40)	0.26		-
81	Yi 2018	PAR post-treatment	MD:1.03 (-0.27,2.33)	0.12		-
82	Yi 2018	PAR reduction	MD:-2.46 (-5.44,0.52)	0.11		-
83	Yi 2018	EARR (total)	MD:-1.84 (-2.35,-1.33)	<0.001	3.67	No
84	Yi 2018	EARR (maxillary central incisors)	MD:-1.13 (-2.20,-0.06)	0.04	3.90	No
85	Yi 2018	EARR (maxillary lateral incisors)	MD:-1.76 (-2.84,-0.68)	0.001	3.86	No
86	Yi 2018	EARR (mandibular central incisors)	MD:-1.15 (-2.07,-0.23)	0.02	3.52	No
87	Yi 2018	EARR (mandibular lateral incisors)	MD:-3.30 (-4.24,-2.36)	<0.001	3.34	No

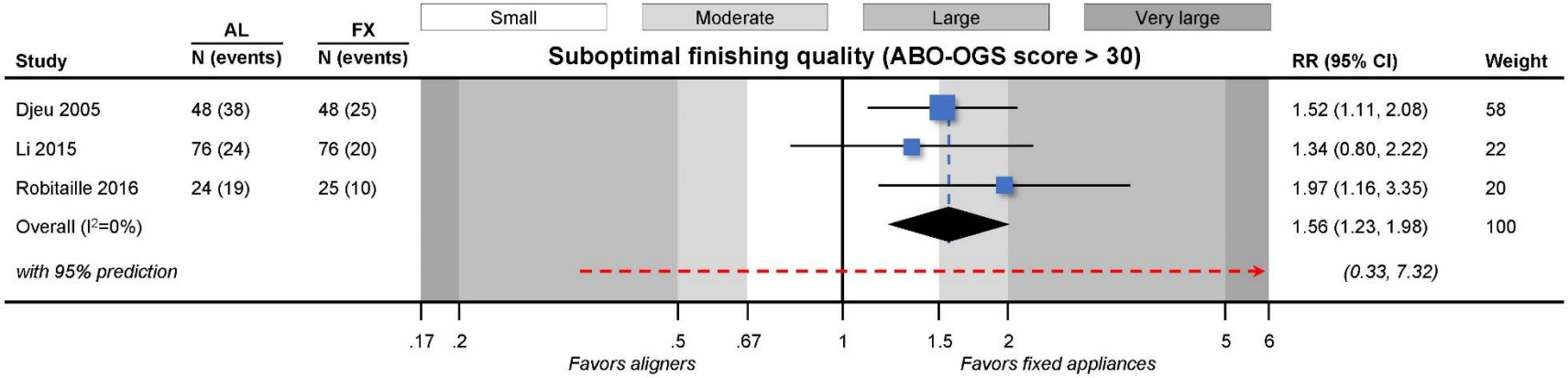
ABO-OGS, objective grading system of the American Board of Orthodontics; CI, confidence interval; EARR, external apical root resorption; MD, mean difference; PAR, peer assessment rating; PPD, periodontal probing depth; Rel, clinically relevant (judged as MDs greater than one standard deviation of the control group / RR > 2.0 or RR < 0.5); RR, relative risk; SD, standard deviation in the control group (fixed appliances)

Supplementary Table8. Sensitivity analysis by omitting non-randomized studies.

	Original analysis				Sensitivity analysis		
Outcome	**n**	**Effect (95% CI)**	**P**		**n**	**Effect (95% CI)**	**P**
Treatment duration (months)	7	MD: -0.55 (-3.73, 2.63)	0.73		2	MD: 2.69 (-4.97, 10.35)	0.49
ABO-OGS total score	**3**	**MD: 9.91 (3.62, 16.21)**	**0.002**		**1**	**MD: 4.38 (2.20, 6.56)**	**<0.001**
ABO-OGS failure (score>30)	**3**	**RR: 1.56 (1.23, 1.98)**	**<0.001**		1	RR: 1.34 (0.80, 2.23)	0.27
ABO-OGS component: alignment	3	MD: 1.59 (-1.05, 4.22)	0.24		1	MD: -0.38 (-1.54, 0.78)	0.52
ABO-OGS component: marginal ridges	3	MD: 0.46 (-0.18, 1.10)	0.16		1	MD: 0.25 (-0.77, 1.27)	0.63
ABO-OGS component: buccolingual inclination	**3**	**MD: 0.78 (0.46,1.09)**	**<0.001**		**1**	**MD: 0.73 (0.40, 1.06)**	**<0.001**
ABO-OGS component: occlusal contacts	**3**	**MD: 3.07 (0.57, 5.57)**	**0.02**		1	MD: 0.93 (-0.29, 2.15)	0.13
ABO-OGS component: occlusal relationship	**3**	**MD: 0.99 (0.58, 1.40)**	**<0.001**		**1**	**MD: 0.95 (0.52, 1.38)**	**<0.001**
ABO-OGS component: overjet	**3**	**MD: 1.81 (0.64, 2.98)**	**0.002**		**1**	**MD: 1.15 (0.48, 1.82)**	**0.001**
ABO-OGS component: interproximal contacts	3	MD: 0.02 (-0.16, 0.21)	0.82		1	MD: 0.05 (-1.26, 1.36)	0.94
ABO-OGS component: root angulation	**3**	**MD: 0.79 (0.49, 1.10)**	**<0.001**		**1**	**MD: 0.70 (0.25, 1.15)**	**0.002**
PAR post-Tx	2	MD: -0.03 (-2.02, 1.96)	0.98		0	-	
PAR reduction via Tx	3	MD: -1.76 (-3.62, 0.10)	0.06		0	-	

ABO-OGS, objective grading system of the American Board of Orthodontics; CI, confidence interval; MD, mean difference; PAR, peer assessment rating; RR, relative risk; Tx, treatment.

Supplementary Fig 1. Contour-enhanced forest plot on the comparison of proportion of 'passing' cases according to the ABO examination (cases with ABO-OGS score lower than 30 points) post-treatment between aligners and fixed appliances. ABO-OGS, American Board of Orthodontists Objective Grading System; AL, aligner; CI, confidence interval; FX, fixed appliance; N, number of patients; RR, relative risk. Contours correspond to different effect magnitude and the red dotted line corresponds to 95% random-effects prediction.



Supplementary Fig 2. Illustration of the expected absolute risk for a case to have an ABO-OGS score of over 30 post debond when treated with aligners or fixed appliances, according to the results of the meta-analysis. ABO, American Board of Orthodontists.